Year : 2019

The role of intermediate factors and biological mechanisms in life-course socioeconomic differences in cardiometabolic disorders

Petrovic Dusan

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

UNISANTÉ

Institut Universitaire de Médecine Sociale et Préventive
Département d'Épidémiologie et Systèmes de Santé

The role of intermediate factors and biological mechanisms in life-course socioeconomic differences in cardiometabolic disorders

Thèse de doctorat ès sciences de la vie (PhD)
présentée à la
Faculté de biologie et de médecine
de l'Université de Lausanne
par

Dusan PETROVIC
Biologiste diplômé de l'Université de Lausanne

Jury
Prof. Lazare Benaroyo, Président
Prof. Murielle Bochud, Directrice de thèse
Dre Silvia Stringhini, Co-directrice de thèse
Prof. Brigitte Santos-Eggimann, Experte
Prof. Antoine Flahault, Expert

Lausanne, 2019

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

UNISANTÉ

Institut Universitaire de Médecine Sociale et Préventive
Département d'Épidémiologie et Systèmes de Santé

The role of intermediate factors and biological mechanisms in life-course socioeconomic differences in cardiometabolic disorders

Thèse de doctorat ès sciences de la vie (PhD)
présentée à la
Faculté de biologie et de médecine
de l'Université de Lausanne
par

Dusan PETROVIC
Biologiste diplômé de l'Université de Lausanne

Jury
Prof. Lazare Benaroyo, Président
Prof. Murielle Bochud, Directrice de thèse
Dre Silvia Stringhini, Co-directrice de thèse
Prof. Brigitte Santos-Eggimann, Experte
Prof. Antoine Flahault, Expert

Lausanne, 2019

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président·e	Monsieur	Prof.	Lazare	**Benaroyo**
Directeur·trice de thèse	Madame	Prof.	Murielle	**Bochud**
Co-directeur·trice	Madame	Dre	Silvia	**Stringhini**
Expert·e·s	Madame	Prof.	Brigitte	**Santos-Eggimann**
	Monsieur	Prof.	Antoine	**Flahault**

le Conseil de Faculté autorise l'impression de la thèse de

Monsieur Dusan Petrovic

Maîtrise universitaire en biologie médicale , Université de Lausanne

intitulée

The role of intermediate factors and biological mechanisms in life-course socioeconomic differences in cardiometabolic disorders

Lausanne, le 18 décembre 2019

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Lazare Benaroyo

Table of contents

Acknowledgments

The completion of this thesis would not have been possible without the support and encouragements of several people. First, I would like to express my immense gratitude to my supervisors, Prof. Murielle Bochud and Dr. Silvia Stringhini for accepting me as a PhD student, and for their guidance, trust, and constant support throughout these four years. Their scientific expertise, commitment and passion for epidemiologic research are an inspiration to me. I would also like to thank Dr. Marc Chadeau-Hyam for his invitation at Imperial College London. I particularly appreciated his professional guidance, expertise in the OMICS field, and his positive attitude during my one year stay in London. I am also grateful to the Swiss National Science Foundation for giving me the opportunity to realize this one year Doc.Mobility fellowship. I would also like to thank all the members of the Lifepath project with whom I collaborated throughout my PhD, as well as all the collaborators who provided extensive contribution while realizing the chapters of this thesis and my other research projects.

I would also like to thank all my colleagues and friends with whom I shared these years at the IUMSP and who made every day at work enjoyable; especially Carlos de Mestral, Saman Khalatbari-Soltani, Angéline Châtelan, Sandrine Estoppey-Younès, Zhenyu Zhang, Fabiën Belle, Claire Zuppinger, Cristian Carmeli, Jean-Pierre Ghobril, Patricia Dumas, Alex Randriamiharisoa, and all the other members of the DMC. I feel extremely grateful to have met them.

Finally, I would like to thank my fiancée, Julie, for her unconditional support, love, and for being my other half during the last three years, and my family and friends for their encouragements, presence, and support throughout my PhD.

Affiliations of the PhD committee members

Director:	Prof. Murielle Bochud, Centre universitaire de médecine Générale et santé publique (UNISANTÉ), Institute of Social and Preventive Medicine (IUMSP), Lausanne, Switzerland
Co-Director:	Dr. Silvia Stringhini, Unit of Population Epidemiology, Primary Care Division, Geneva University Hospital, Geneva, Switzerland Department of Epidemiology and Health Systems Centre universitaire de médecine Générale et santé publique (UNISANTÉ), Institute of Social and Preventive Medicine (IUMSP), Lausanne, Switzerland
Expert:	Prof. Brigitte Santos-Eggimann, Unit of Health Services (USS) Centre universitaire de médecine Générale et santé publique (UNISANTÉ), Institute of Social and Preventive Medicine (IUMSP), Lausanne, Switzerland
External expert:	Prof. Antoine Flahault, Institute of Global Health, University of Geneva, Geneva, Switzerland
President:	Prof. Lazare Benaroyo, FTSR, Centre interdisciplinaire de recherché en éthique (CIRE) Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

List of publications

Publication	Author contribution	Status
Petrovic D, Haba – Rubio J, de Mestral C, Kelly-Irving M, Vineis P, Kivimaki M, Nyberg S, Gandini M, Bochud M, Vollenweider P, d'Errico A, Barros H, Fraga S, Goldberg M, Zins M, Steptoe A, Delpierre C, Heinzer R, Carmeli C, Chadeau-Hyam M, Stringhini S. *The contribution of sleep to social inequalities in cardiovascular disorders: a multi-cohort study.* **Cardiovascular research (IF=7.014)**	PD, SS, CC, and ChM M designed the study. PD performed the statistical analyses, NyS performed the longitudinal analyses. PD wrote the manuscript. PD, HRJ, dMC, KI-Mic, KiMi, NyS, GS, BM, VP, d'EA, BH, FS, GM, ZM, SA, DC, HR, CC, ChM M, SS critically revised the manuscript	Published
Petrovic D, Haba - Rubio J, Carmeli C, Vollenweider P, Heinzer R, Stringhini S. *Social inequalities in sleep - disordered breathing: Evidence from the CoLaus| HypnoLaus study.* **J Sleep Res (IF=3.433)**. 2018;e12799.	SS, HR, HRJ, PD designed the study. PD and SS performed the statistical analyses. PD wrote the manuscript. PD, SS, HR, HRJ, VP critically revised the manuscript	Published
Petrovic D, de Mestral C, Bochud M, Bartley M, Kivimäki M, Vineis P, Mackenbach J, Stringhini S. *The contribution of health behaviors to socioeconomic inequalities in health: A systematic review.* **Preventive Medicine (IF=3.483)** 2018;113:15-31.	PD and SS designed the study. PD and dMC performed the literature review. PD performed the analyses, synthesized findings, wrote the manuscript. PD, SS, dMC, BoM, BaM, KM, VP, MJ critically revised the manuscript	Published
Petrovic D, Pivin E, Ponte B, Dhayat N, Pruijm M, Ehret G, Ackermann D, Guessous I, Estoppey Younes S, Pechère-Bertschi A, Vogt B, Mohaupt M, Martin PY, Paccaud PY, Burnier M, Bochud M and Stringhini S. *Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study.* **Psychoneuroendocrinology (IF=4.788)**. 2016;67:76-85.	PD and SS designed the study. PD performed the main statistical analyses, PE analysed the heritability of allostatic load. PD wrote the manuscript. PD, SS, PE, PB, AD, GI, EYS, PBA, MM, MP, PY, BuM, BoM, BoM, BaM, KM, VP, MJ critically revised the manuscript	Published

Petrovic D, Younes SE, Pruijm M, Ponte B, Ackermann D, Ehret G, Ansermot N, Mohaupt M, Paccaud F, Vogt B, Pechère-Bertschi A, Martin PY, Burnier M, Eap CB, Bochud M and Guessous I. *Relation of 24-hour urinary caffeine and caffeine metabolite excretions with self-reported consumption of coffee and other caffeinated beverages in the general population.* **Nutrition & metabolism (IF=2.974)** 2016;13(1):81.	BoM, GI, and PD designed the study. PD performed the statistical analyses and wrote the manuscript. PD, YSE, PM, PB, EG, AN, MM, PF, VB, PBA, MPY, BuM, ECH, BoM critically revised the manuscript	Published
de Mestral C, Mayén A-L**, Petrovic D**, Marques-Vidal P, Bochud M, Stringhini S. *Socioeconomic Determinants of Sodium Intake in Adult Populations of High-Income Countries: A Systematic Review and Meta-Analysis***.** American journal of public health **(IF= 4.552)**. 2017;107(4):e1-e12.	dMC and SS generated the idea and analytical plan. dMC, MAL and PD conducted literature search and extracted data. dMC wrote the manuscript, on which all coauthors commented.	Published
Petrovic D, Carmeli C, Bodinier B, Chadeau-Hyam M, Ehret G, Ponte B, Dhayat N, Pruijm M, Dermitzakis E, Bochud M, Stringhini S. *Exploring the relation between life-course socioeconomic position and genome-wide CpG DNA methylation in a Swiss-population based study*	SS, BM, PD, CC designed the study. PD performed the statistical analyses and wrote the manuscript. CC, BB, CHM, EG, PB, DN, PM, DE, BM, and SS critically revised the manuscript.	With co-authors

List of communications

Event and location	Presentation format
European Public Health Conference, Nov 2018, Ljubljana. Petrovic D, Haba-Rubio J, Carmeli C, Vollenweider P, Heinzer R, Stringhini S. *Social inequalities in sleep-disordered breathing: evidence from the CoLaus|HypnoLaus study.*	Oral
Swiss Public Health Conference, Nov 2018, Neuchâtel. Petrovic D, Haba-Rubio J, Carmeli C, Vollenweider P, Heinzer R, Stringhini S. *Social inequalities in sleep-disordered breathing: evidence from the CoLaus|HypnoLaus study.*	Oral
Swiss Public Health Conference, Nov 2017, Basel. Petrovic D, Haba-Rubio J, Kelly Irving M, Carmeli C, Chadeau-Hyam M, Vineis P, Kivimaki M, Gandini M, Bochud M, Vollenweider P, d'Errico A, Barros H, Fraga S, Goldberg M, Zins M, Steptoe A, Delpierre C, Heinzer R, Stringhini S. *The contribution of sleep to social inequalities in cardiovascular disorders: a multi-cohort study.*	Oral
Swiss Public Health Conference, Nov 2017, Basel. Petrovic D, de Mestral C, Bochud M, Bartley M, Kivimaki M, Vineis P, Mackenbach J and Stringhini S. *The contribution of health behaviors to socioeconomic inequalities in health: a systematic review*	Oral
The Association of Schools of Public Health in the European Region – European Public Health Conference, Nov 2017, Stockholm. Petrovic D, Haba-Rubio J, Kelly Irving M, Carmeli C, Chadeau-Hyam M, Vineis P, Kivimaki M, Gandini M, Bochud M, Vollenweider P, d'Errico A, Barros H, Fraga S, Goldberg M, Zins M, Steptoe A, Delpierre C, Heinzer R, Stringhini S. *The contribution of sleep to social inequalities in cardiovascular disorders: a multi-cohort study.*	Oral
Swiss Public Health Conference Sep 2015, Geneva Petrovic D, Pivin E, Ponte B, Dhayat N, Pruijm M, Ehret G, et al. *Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study.*	Poster

List of grants and awards

1. *Doc.Mobility Fellowship* P1LAP_178061, 2018, awarded by the Swiss National Science Foundation to conduct research at Imperial College London as a visiting research student for the duration of 12 monts (CHF 56000)
2. *Travel grant* from the Fondation de l'Université de Lausanne to attend European Public Health Conference in Stockholm, Sweden, 2017 (CHF 1100)

Research work conducted during PhD not part of this thesis

1. *Objective:* To investigate the sociodemographic, behavioral, and genetic determinants of allostatic load in a Swiss population-based study
    - **Petrovic D**, Pivin E, Ponte B, Dhayat N, Pruijm M, Ehret G, Ackermann D, Guessous I, Estoppey Younes S, Pechère-Bertschi A, Vogt B, Mohaupt M, Martin PY, Paccaud PY, Burnier M, Bochud M and Stringhini S. *Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study.* **Psychoneuroendocrinology (IF=4.788)**. 2016;67:76-85.

2. *Objective:* To investigate the socioeconomic patterning of sleep-disordered breathing and to examine the of lifestyle-related factors as potential mediators to this gradient.
    - **Petrovic D**, Haba - Rubio J, Carmeli C, Vollenweider P, Heinzer R, Stringhini S. *Social inequalities in sleep - disordered breathing: Evidence from the CoLaus|HypnoLaus study.* **J Sleep Res (IF=3.433)**. 2018;e12799.

3. *Objective:* To investigate the relation between 24-hour urinary caffeine and caffeine metabolite excretion to self-reported caffeinated beverages in a Swiss population-based study.
    - **Petrovic D**, Younes SE, Pruijm M, Ponte B, Ackermann D, Ehret G, Ansermot N, Mohaupt M, Paccaud F, Vogt B, Pechère-Bertschi A, Martin PY, Burnier M, Eap CB, Bochud M and Guessous I. *Relation of 24-hour urinary caffeine and caffeine metabolite excretions with self-reported consumption of coffee and other caffeinated beverages in the general population.* **Nutrition & metabolism (IF=2.974)** 2016;13(1):81.

4. *Objective:* To investigate the relation between lung cancer and genome-wide DNA methylation changes using univariate, multivariate, and network approaches
    - **Petrovic D,** Bodinier B, Karimi M, Guida F, Campanella G, Nost T, Polidoro S,Palli D, Krogh V, tumino R, Sacerdote C, Panico S, Lund E, Vineis P, Sananger T, Vermeulen R, Chadeau Hyam-M. *Exploring the association between epigenome-wide DNA methylation in relation with lung cancer status in EPIC-Italy and NOWAC population-based studies.*

      Manuscript and statistical analyses achieved. Under examination by co-authors

5. *Objective:* To systematically investigate socioeconomic determinants of sodium intake in high income countries.
    - de Mestral C, Mayén A-L**, Petrovic D**, Marques-Vidal P, Bochud M, Stringhini S. *Socioeconomic Determinants of Sodium Intake in Adult Populations of High-Income Countries: A Systematic Review and Meta-Analysis***.** American journal of public health **(IF= 4.552)**. 2017;107(4):e1-e12.

Summary

Individuals experiencing adverse socioeconomic circumstances across the life-course are disproportionately affected by cardiometabolic diseases (CMD) in high income countries. While these inequalities have resulted from the epidemiological transition whereby the "diseases of affluence" have become the "diseases of the poor", the exact mechanisms underlying the life-course socioeconomic gradient in cardiometabolic disorders are only partially understood. The purpose of this thesis was to investigate the contribution of intermediate factors and the role of biological processes to the association between life-course socioeconomic position (SEP) and cardiometabolic disorders. In the first part of this thesis, we performed a systematic review of the literature examining the contribution of health behaviors to socioeconomic differences in cardiometabolic disorders and all-cause mortality. We found that the role of health behaviors varied according to social, economic, regional, and cultural factors. We identified three explanatory mechanisms for the contribution of health behaviors: the differential social patterning of health behaviors, physiological factors, and methodological characteristics of included studies. In the second part of this thesis, we investigated the contribution of sleep duration as an additional, unexplored intermediate factors of the life-course socioeconomic gradient in cardiovascular disorders. We observed a strong association between low socioeconomic position and abnormal sleeping duration patterns, but also a strong association between poor sleep and an increased cardiovascular risk. Moreover, we found that sleep duration meaningfully contributed to the life-course socioeconomic differences in cardiovascular disorders, explaining up to 13% of this gradient. Finally, we examined the associations between nine indicators of life-course SEP and DNA methylation of 451'000 epigenome-wide CpG markers. We identified 161 CpGs related to three SEP indicators in adulthood, and found that the identified CpGs were involved in inflammatory, immune, and cancer-related processes. In summary, the findings presented in this thesis contribute to a more complete understanding of the mechanisms underlying the life-course socioeconomic differences in cardiometabolic disorders; however, further research is needed to identify all potential intermediate mechanisms, and to characterize their overall role in shaping the socioeconomic gradient in health-related outcomes.

Résumé

Dans les pays riches, les individus éprouvant des circonstances socioéconomiques défavorables au cours de leurs vies sont affectés de façon disproportionnée par des troubles cardiométaboliques. Alors que ces inégalités ont résulté de la transition épidémiologique où les « maladies de l'opulence » sont devenues les « maladies du pauvre », les mécanismes sous-jacents au gradient socioéconomique dans les troubles cardiométaboliques sont peu connus. L'objectif de cette thèse était d'investiguer la contribution des facteurs intermédiaires et le rôle des processus biologiques dans l'association entre la position socioéconomique (PSE) à travers le parcours de vie et les troubles cardiométaboliques. Dans la première partie de cette thèse, nous avons réalisé une revue systématique de littérature examinant la contribution des comportements de santé aux différences socioéconomiques dans les troubles cardiométaboliques et la mortalité. Nous avons trouvé que la contribution des comportements de santé variait suivant des facteurs sociaux, économiques, régionaux et culturels. Nous avons identifié trois mécanismes explicatifs quant à cette contribution hétérogène des comportements de santé : la distribution sociale différentielle des comportements de santé, les facteurs physiologiques et les aspects méthodologiques des articles inclus. Dans la deuxième partie de cette thèse, nous avons exploré la contribution de la durée du sommeil en tant que facteur intermédiaire de l'association entre la PSE à travers le parcours de vie et les troubles cardiovasculaires. Nous avons observé une forte association entre une PSE basse et une durée du sommeil anormale, mais aussi une forte association entre un sommeil perturbé et un risque cardiovasculaire plus élevé. Par ailleurs, nous avons trouvé que la durée du sommeil contribuait de façon significative à l'association entre la PSE à travers le parcours de vie et les troubles cardiovasculaires, expliquant jusqu'à 13% de cette relation. Finalement, nous avons examiné l'association entre neuf indicateurs de la PSE à travers le parcours de vie et la methylation de 451'000 marqueurs CpG à travers l'épigénome. Nous avons identifié 161 CpGs associés avec la PSE dans la vie adulte, et avons trouvé que ces CpGs étaient impliqués dans des processus liés à l'inflammation, au système immunitaire, et au cancer. En résumé, les résultats obtenus dans cette thèse contribuent à une compréhension plus complète des mécanismes sous-jacents aux différences socioéconomiques dans les troubles cardiométaboliques ; cependant, des investigations supplémentaires sont nécessaires afin d'identifier tous les mécanismes intermédiaires et de caractériser leur contribution globale au gradient socioéconomique dans la santé.

List of abbreviations

BAC	*Baccalauréat* – High school diploma (France)
BMI	Body mass index
CI	Confidence interval
CHD	Coronary heart disease
CMD	Cardiometabolic disorder
CpG	Cytosine-Guanine dinucleotide
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
MTE	Marginal total effect
NDE	Natural direct effect
NIE	Natural indirect effect
OR	Odds ratio
PM	Proportion mediated
SD	Standard deviation
SEP	Socioeconomic position
UK	United Kingdom

Introduction

The socioeconomic gradient in cardiometabolic disorders

The existence of a socioeconomic gradient in health has been consistently observed and extensively documented in epidemiological research, whereby individuals with a lower socioeconomic position (SEP), usually measured by occupation, education, or income, experience poorer health and greater mortality than more advantaged individuals [1-3]. While health inequalities have existed ever since the beginning of human societies, the stepwise gradient between socioeconomic circumstances and health started to become evident during the nineteenth century, and was generally attributed to poverty, hazardous jobs, undernutrition, and poor hygiene [1, 4-6].

Throughout the twentieth century, major medical achievements and important progresses in the living and working standards have led to a substantial decline in overall mortality and an increase in life-expectancy in Western countries [7]. While the burden of infectious diseases has been reduced dramatically, the impact of lifestyle-related chronic conditions, such as cardiovascular diseases, metabolic disorders, respiratory illnesses, or cancer, has been steadily increasing since the 1950's [8, 9]. In particular, cardiometabolic disorders (CMD) including obesity, hypertension, hypercholesterolemia, diabetes, and cardiovascular diseases, nowadays constitute the leading cause of death in high income countries and have become an important burden in a large number of low and middle income countries [9-15]. Initially known as the "diseases of affluence", cardiometabolic disorders and their related risk factors were originally more prevalent in the higher socioeconomic groups, whereby conditions such as obesity, and associated behaviors such as smoking, and high-fat, energy-dense diets were reserved to socioeconomically privileged individuals, and perceived as status symbols [16]. However, following major social, economic,

and cultural changes that occurred in the West during the post-war period, cardiometabolic disorders and their related risk factors gradually shifted from the higher towards the lower socioeconomic groups as part of the epidemiological transition, eventually becoming the "diseases of the poor" [8, 16]. The processes underlying this transition included major economic development, which saw products such as tobacco, red meat, animal fats, and highly processed foods become widely available to the overall population [16, 17]. Furthermore, social phenomena also marked this shift, whereby lower socioeconomic groups progressively adopted "innovative", unhealthy behaviors (i.e. smoking) which were originally reserved to the better-off, whereas the upper classes have been better able to adapt their behaviors as the health effects of smoking, poor diet, and physical inactivity became apparent [16-19].

Figure 1 illustrates the graded relation between education and obesity (A), education and mean systolic blood pressure (B), deprivation and diabetes (C), and social disadvantage and infarction mortality (D), in Switzerland, France, and the United Kingdom between 1994 and 2009.

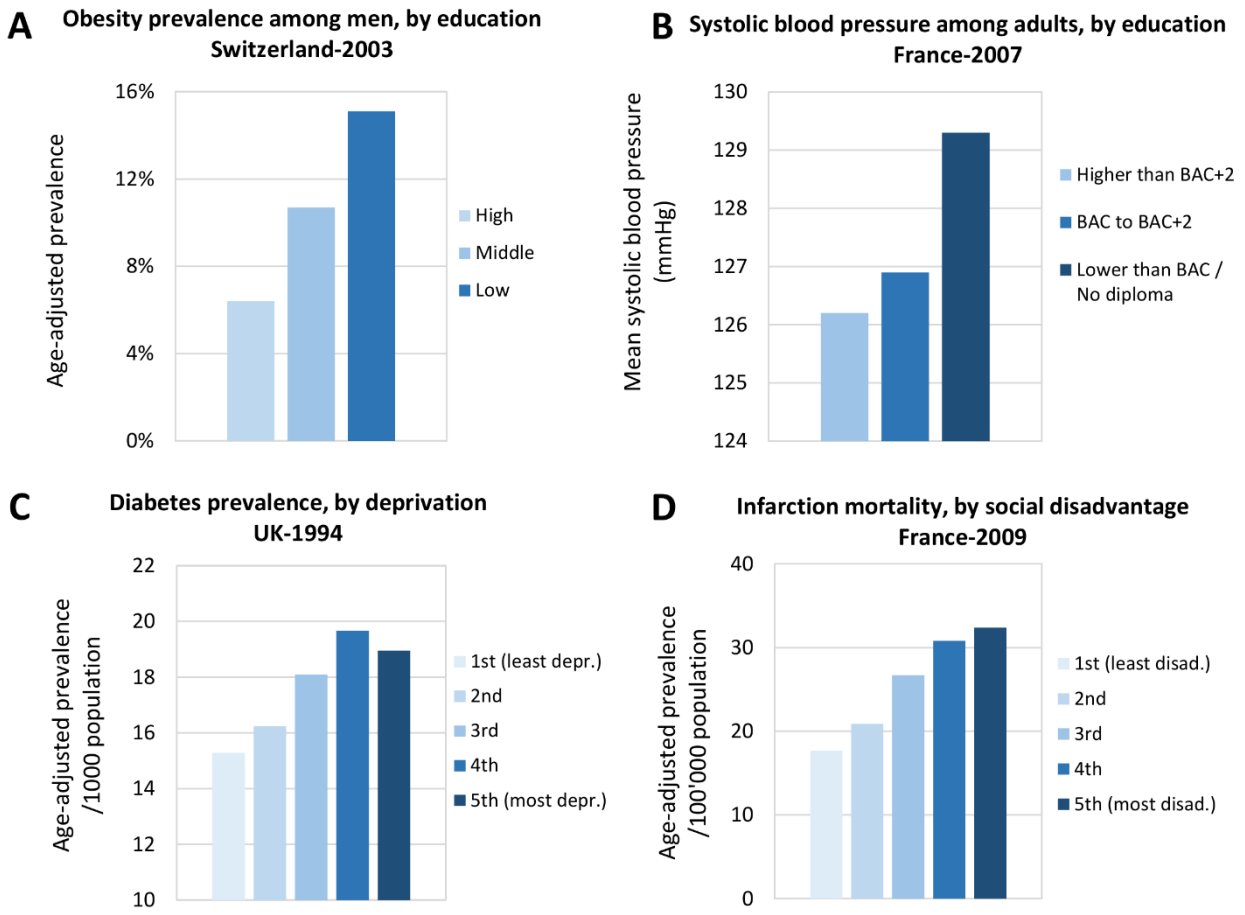


Figure 1

BAC, *Baccalauréat* – High school diploma; BAC+2, two years of additional superior education after *Baccalauréat*

A. Age-adjusted obesity prevalence among men in Switzerland in 2008, by highest attained education. Adapted from [20].

B. Mean systolic blood pressure among adults in France in 2007, by highest attained education. Adapted from [21].

C. Age-adjusted prevalence of diabetes among UK men in 1994, by quintiles of deprivation (1st least deprived, 5th most deprived). Adapted from [22].

D. Age-adjusted prevalence of infarction mortality, by municipality social disadvantage (1st least disadvantaged, 5th most disadvantaged). Adapted from [23].

The life-course perspective on cardiometabolic disorders

An important contribution to the understanding of the development of cardiometabolic disorders came with the "developmental origins of adult disease" hypothesis and the life-course approach in epidemiology, which postulate that environmental, biological, and social exposures across different life periods (gestation, childhood, adolescence, adulthood), alter one's physiology and influence later disease risk [24, 25]. Initially developed following observations that a low birthweight is related to a higher cardiovascular risk in later life, research in life-course epidemiology has shown that early exposures such as fetal undernutrition, maternal obesity, or adverse childhood experiences (i.e. adversity, abuse, parental separation), negatively affect cardiometabolic disease risk in adulthood [24, 26-30]. From the social epidemiology point of view, the importance of the life-course approach came with the research examining the role of early-life socioeconomic factors in later disease occurrence, whereby adverse socioeconomic circumstances in earlier life periods were found to influence the development of obesity, hypercholesterolemia, hypertension, and coronary heart disease in adulthood [31, 32].

The life-course approach combines multiple conceptual models along with the use of longitudinal data, whereby environmental, biological, and socioeconomic factors interact throughout life to influence later health and disease risk. As a result, three main non-mutually exclusive causal models for the life-course perspective in the development of cardiometabolic disorders have been elaborated; the critical period model, the accumulation model, and the pathway model [33, 34]. First, the critical period model implies that there are specific time windows throughout life when the body is particularly sensitive to external exposures (i.e. *in utero* development, the first year of life, adolescence, etc.), which would then result in either protective or adverse effects on future

health. In the context of socioeconomic differences in cardiometabolic disorders, an impaired fetal growth resulting from maternal socioeconomic adversity and malnutrition was found to result in an increased risk of obesity and coronary heart disease in later life [28, 31]. Second, the accumulation model is based on the principle that events characterizing different life periods have an additive effect, whereby adverse exposures, such as successive periods of socioeconomic adversity, accumulate across the life-course and affect later cardiometabolic disease risk in a dose-response manner. Third, the chains of risk, or the pathway model, implies that earlier exposures do not necessarily have physiological effects, but that they may determine later exposures and adverse circumstances, which in turn directly affect health. From the social epidemiology perspective, this may be related to the fact that certain socioeconomic factors in early life do not have direct consequences on cardiometabolic outcomes, but may shape subsequent socioeconomic circumstances which in turn determine later cardiometabolic disorders [33]. While, these causal models may present important conceptual differences, former investigations have shown that they actually all contribute to the life-course socioeconomic differences in cardiometabolic disorders, and should be considered as complementary in shaping this gradient [35].

The role of intermediate mechanisms in the life-course socioeconomic gradient in cardiometabolic disorders

Along with the life-course perspective, previous research has also led to the development of a conceptual framework incorporating intermediate factors ("middle layer"), and subsequent biological processes ("inner layer") to the causal pathway between life-course socioeconomic circumstances and the occurrence of cardiometabolic disorders (**Figure 2**) [10, 36, 37]. Intermediate factors including patterns of unhealthy behaviors, chronic toxic environmental exposures, psychosocial stressors, and limited access or use of health care, are generally considered as mediators of the socioeconomic gradient in cardiometabolic disorders, as they are globally determined by socioeconomic factors, but are also known to affect subsequent physiological processes leading to a higher cardiometabolic disease risk [36, 38].

Health behaviors including tobacco use, physical activity, dietary patterns, and alcohol intake have been the object of particular attention in epidemiological research [38-40]. Previous studies conducted in Western countries have shown that smoking, sedentary behavior, and inadequate diet, have been steadily increasing in the lower socioeconomic groups since the 1950's, eventually resulting in a much higher prevalence of these unhealthy behaviors among the less well-off [16]. Furthermore, the adverse effects of these unhealthy behaviors on cardiometabolic outcomes have been extensively demonstrated in former clinical and epidemiological investigations, with smoking being a major risk factor for coronary heart disease, and high-fat, energy-dense diets and physical inactivity leading to diabetes, obesity, hypertension, and cardiovascular events [34, 36, 39-41]. As a result, it has been suggested that health behaviors are important intermediate factors of the socioeconomic gradient in cardiometabolic disorders;

however, their overall contribution to this gradient was found to vary substantially across previous studies [38]. Psychosocial factors are also considered as important mediators of the socioeconomic gradient in health, whereby poor material, financial, or social circumstances lead to higher levels of stress, more negative life events, fewer psychosocial resources, allowing to deal with daily hassles [17]. Subsequently, long-term chronic stress and the perception of various threats and burdens across the life-course permanently affect multiple mental, behavioral, and physiological processes, eventually leading to higher rates of depression, diabetes, obesity, and cardiovascular diseases [17, 36, 42, 43]. Environmental exposures constitute another important group of mediators, whose contribution to the socioeconomic gradient in health was already proposed during the nineteenth century, when the adverse living, working and sanitary conditions were seen as the main reason for this gradient [36, 44]. The environmental exposure hypothesis implies that socioeconomically disadvantaged individuals are not only more exposed to environmental hazards such as toxins, pollutants, and noise, but also to deprived neighborhoods and communities characterized by poor housing, insecurity, and insufficient access to healthy food and green spaces, which adversely affect cardiometabolic and other health-related outcomes [36, 45]. Furthermore, it has also been suggested that access and use of health care services could be another mediator of the socioeconomic gradient in cardiometabolic disorders and other health outcomes, particularly in countries that do not provide universal health care coverage, or that lack the resources to maintain effective public health care services [3, 34, 46, 47]. Finally, the contribution of other unknown mediators to the life-course socioeconomic gradient in cardiometabolic disorders cannot be discarded. In particular, recent investigations have suggested that sleep-related patterns, including sleep duration, sleep quality, and sleep apnea, may mediate the socioeconomic gradient in cardiometabolic disorders, as sleep was found to be determined by

socioeconomic factors, but also to affect multiple physiological processes, including glucose intolerance, hypertension, and the occurrence of cardiovascular events [48-51].

The role of biological pathways in the life-course socioeconomic gradient in cardiometabolic disorders

Along with the role of intermediate factors, former research has investigated series of biological mechanisms through which adverse socioeconomic circumstances and their associated risk factors potentially "get under the skin" and affect later cardiometabolic disease risk [36].

Among the most cited underlying biological pathways is the Hypothalamus-Pituitary-Adrenal axis (HPA), which controls the long-term stress response by regulating the release of corticosteroid hormones. Former investigations have suggested that in situations of chronic stress or prolonged adversity, the HPA axis is no longer properly regulated, eventually resulting in the release of excessive amounts of corticosteroids, which in turn affect multiple biological processes [34]. While mineralocorticoids such as aldosterone cause an increase of blood pressure and may result in hypertension, glucocorticoids such as cortisol promote glucose and fatty acid release, insulin resistance, protein degradation, and immunosuppression, altogether favoring obesity, diabetes, hypercholesterolemia, and cardiovascular events [36, 52]. The alterations of neurological structures constitute another potential biological pathway of the "social embedding" [36]. Former research has shown that the experience of adverse life events and poor socioeconomic circumstances may affect the adequate functioning of brain structures such as the amygdala or locus coeruleus, which in turn exacerbate the perception of threats, negative emotions, and feelings of powerlessness, eventually resulting in depression, cardiovascular diseases, and other disorders, in part via unhealthy behaviors (e.g. difficulty to control appetite

and make healthy dietary choices) [17, 36, 43, 53]. Moreover, disrupted inflammatory patterns have also been proposed as biological pathways underlying socioeconomic differences in health, whereby social adversity and unhealthy behaviors lead to elevated levels of pro-inflammatory markers such as C-reactive protein (CRP), cytokines, fibrinogen, or white blood cell infiltration, which have been related to autoimmune diseases, diabetes, and atherosclerosis [54-57]. In addition to the role of distinct or separate biological pathways, epidemiological studies have been increasingly using the concept of allostatic load (AL) since the 1990's, which is an indicator of generalized physiological dysregulation resulting from chronic psychosocial or physical challenges, and which incorporates markers from multiple biological systems and processes (cardiovascular, metabolic, HPA, dyslipidemic, inflammatory, oxidative stress) [58-60]. While allostatic load was found to be driven by poor socioeconomic circumstances and to influence later cardiometabolic disease risk, one of the major strength of this composite indicator is that it offers a global perspective of multiple, subclinical alterations caused by adversity, unhealthy behaviors, and chronic stress [61, 62]. Finally, evidence has been accumulating for the role of epigenetic modifications as an additional mechanism of social embedding [63, 64]. Former research has suggested that adverse environmental or psychosocial stimuli may lead to differential DNA methylation, whereby methyl groups are added to Cytosine nucleotides within specific DNA sequences [52]. Whilst DNA methylation does not change the DNA sequence, this process may lead to a differential expression of genes controlling key biological pathways, such as inflammation and the regulation of the HPA axis, eventually affecting cardiometabolic disease risk [63].

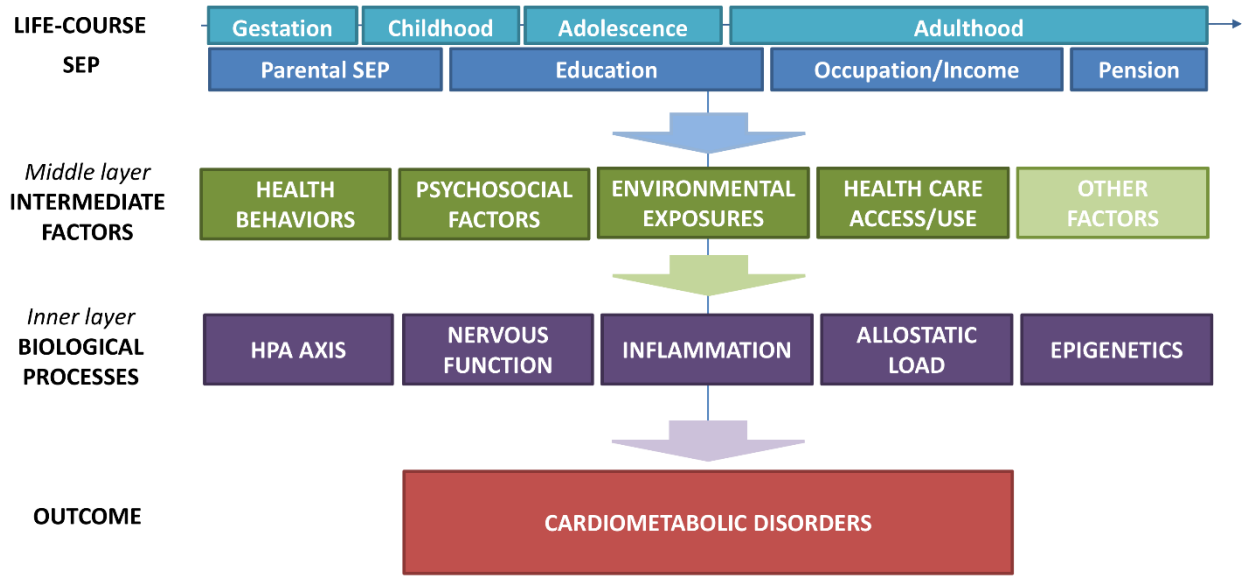


Figure 2
HPA, Hypothalamus-Pituitary-Adrenal axis; SEP, Socioeconomic position
Conceptual framework representing the association between life-course SEP and health-related outcomes, along with intermediate mechanisms: middle layer intermediate risk factors and inner layer biological pathways. Adapted from [11, 36, 65].

Thesis objectives

Despite the development of an extended conceptual framework encompassing multiple mechanisms underlying the life-course socioeconomic gradient in cardiometabolic disorders, the exact role of these intermediate factors and biological processes have often been unclear in previous epidemiological studies. In particular, evidence is lacking regarding the mechanisms driving the differential contribution of health behaviors; the potential contribution of additional, unknown intermediate factors; and a thorough characterization of underexplored biological processes involved in the "embedding" of the social environment.

Thus, the main objectives of this thesis were:

1. To systematically review existing evidence on the contribution of health behaviors to the socioeconomic gradient in cardiometabolic disorders and all-cause mortality.
2. To assess the role of underexplored mechanisms, such as sleep behaviors, in shaping life-course socioeconomic differences in cardiovascular outcomes.
3. To investigate inner layer biological pathways linking life-course socioeconomic circumstances and cardiometabolic disorders.

References

1. Antonovsky, A., *Social class, life expectancy and overall mortality.* The Milbank Memorial Fund Quarterly, 1967. **45**(2): p. 31-73.
2. Krieger, N., D.R. Williams, and N.E. Moss, *Measuring social class in US public health research: concepts, methodologies, and guidelines.* Annual review of public health, 1997. **18**(1): p. 341-378.
3. Adler, N.E., et al., *Socioeconomic inequalities in health. No easy solution.* JAMA, 1993. **269**(24): p. 3140-5.
4. Engels, F. and F.K. Wischnewetzky, *The condition of the working-class in England in 1844: With preface written in 1892*. 2010: Cambridge University Press.
5. Virchow, R.L.K. and L.J. Rather, *Collected essays on public health and epidemiology*. Vol. 1. 1985: Science History Publications, USA.
6. Drever, F. and M. Whitehead, *Health inequalities: decennial supplement.* 1997.
7. Mackenbach, J.P., *Health inequalities: Europe in profile*. 2006: Produced by COI for the Department of Health.
8. Omran, A.R., *The epidemiologic transition: a theory of the epidemiology of population change.* The Milbank Quarterly, 2005. **83**(4): p. 731-757.
9. Gordis, L., *Epidemiology*. Fifth edition ed, ed. E. Saunders. 2014, Philadelphia, PA.
10. Marmot, M., *Social determinants of health inequalities.* The Lancet, 2005. **365**(9464): p. 1099-1104.
11. Imkampe, A.K. and M.C. Gulliford, *Increasing socio-economic inequality in type 2 diabetes prevalence—repeated cross-sectional surveys in England 1994–2006.* The European Journal of Public Health, 2011. **21**(4): p. 484-490.
12. Guessous, I., et al., *Prevalence of frailty indicators and association with socioeconomic status in middle-aged and older adults in a Swiss region with universal health insurance coverage: a population-based cross-sectional study.* Journal of aging research, 2014. **2014**.
13. Mensah, G.A. and D.W. Brown, *An overview of cardiovascular disease burden in the United States.* Health affairs, 2007. **26**(1): p. 38-48.
14. King, H., R.E. Aubert, and W.H. Herman, *Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections.* Diabetes care, 1998. **21**(9): p. 1414-1431.
15. Boutayeb, A. and S. Boutayeb, *The burden of non communicable diseases in developing countries.* International journal for equity in health, 2005. **4**(1): p. 2.
16. Wilkinson, R.G., *The epidemiological transition: from material scarcity to social disadvantage?* Daedalus, 1994: p. 61-77.
17. Marmot, M., *The health gap: the challenge of an unequal world*. 2015: Bloomsbury Publishing.
18. Rogers, E.M., *Diffusion of innovations*. 2010: Simon and Schuster.
19. Beydoun, M.A. and Y. Wang, *Do nutrition knowledge and beliefs modify the association of socio-economic factors and diet quality among US adults?* Preventive medicine, 2008. **46**(2): p. 145-153.
20. Stringhini, S., et al., *Age and gender differences in the social patterning of cardiovascular risk factors in Switzerland: the CoLaus study.* PloS one, 2012. **7**(11): p. e49443.
21. Chaix, B., et al., *Individual/neighborhood social factors and blood pressure in the RECORD cohort study which risk factors explain the associations?* Hypertension, 2010. **55**(3): p. 769-775.
22. Connolly, V., et al., *Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas.* Journal of Epidemiology & Community Health, 2000. **54**(3): p. 173-177.
23. Lecoffre, C., E. Decool, and V. Olié, *Mortalité cardio-neuro-vasculaire et désavantage social en France en 2011.* Bull Epidémiol Hebd, 2016. **20**(21): p. 352-8.

24. Barker, D.J.P., *The developmental origins of adult disease.* Journal of the American College of Nutrition, 2004. **23**(sup6): p. 588S-595S.
25. Barker, D.J. and C. Osmond, *Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales.* The Lancet, 1986. **327**(8489): p. 1077-1081.
26. Rogers, L.K. and M. Velten, *Maternal inflammation, growth retardation, and preterm birth: insights into adult cardiovascular disease.* Life sciences, 2011. **89**(13-14): p. 417-421.
27. De Boo, H.A. and J.E. Harding, *The developmental origins of adult disease (Barker) hypothesis.* Australian and New Zealand Journal of Obstetrics and Gynaecology, 2006. **46**(1): p. 4-14.
28. Roseboom, T.J., et al., *Hungry in the womb: what are the consequences? Lessons from the Dutch famine.* Maturitas, 2011. **70**(2): p. 141-145.
29. Boney, C.M., et al., *Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus.* Pediatrics, 2005. **115**(3): p. e290-e296.
30. Su, S., et al., *The role of adverse childhood experiences in cardiovascular disease risk: a review with emphasis on plausible mechanisms.* Current cardiology reports, 2015. **17**(10): p. 88.
31. Lynch, J. and G.D. Smith, *A life course approach to chronic disease epidemiology.* Annu. Rev. Public Health, 2005. **26**: p. 1-35.
32. Galobardes, B., J.W. Lynch, and G. Davey Smith, *Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation.* Epidemiologic reviews, 2004. **26**(1): p. 7-21.
33. Kuh, D., et al., *Life course epidemiology.* Journal of epidemiology and community health, 2003. **57**(10): p. 778.
34. Marmot, M.G. and R.G. Wilkinson, *Social Determinants of Health*. 1999: Oxford University Press.
35. Hallqvist, J., et al., *Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program.* Social science & medicine, 2004. **58**(8): p. 1555-1562.
36. Wolfe, B., W. Evans, and T.E. Seeman, *Biological Consequences of Socioeconomic Inequalities, The*. 2012: Russell Sage Foundation.
37. Stringhini, S., et al., *Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study.* PLoS Med, 2013. **10**(7): p. e1001479.
38. Stringhini, S., et al., *Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts.* PLoS Med, 2011. **8**(2): p. e1000419.
39. Macintyre, S., *The social patterning of exercise behaviours: the role of personal and local resources.* British Journal of Sports Medicine, 2000. **34**(1): p. 6-6.
40. Wardle, J. and A. Steptoe, *Socioeconomic differences in attitudes and beliefs about healthy lifestyles.* Journal of epidemiology and community health, 2003. **57**(6): p. 440-443.
41. Laaksonen, M., et al., *Income and health behaviours. Evidence from monitoring surveys among Finnish adults.* Journal of Epidemiology and Community Health, 2003. **57**(9): p. 711-717.
42. Matthews, K.A., L.C. Gallo, and S.E. Taylor, *Are psychosocial factors mediators of socioeconomic status and health connections?* Annals of the New York Academy of Sciences, 2010. **1186**(1): p. 146-173.
43. O'Connor, S.G., et al., *Within-subject effects of environmental and social stressors on pre-and post-partum obesity-related biobehavioral responses in low-income Hispanic women: protocol of an intensive longitudinal study.* BMC public health, 2019. **19**(1): p. 253.

44. Morello-Frosch, R. and E.D. Shenassa, *The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities.* Environmental health perspectives, 2006. **114**(8): p. 1150-1153.
45. Næss, Ø., et al., *Air pollution, social deprivation, and mortality: a multilevel cohort study.* Epidemiology, 2007. **18**(6): p. 686-694.
46. Joshi, R., et al., *Global inequalities in access to cardiovascular health care: our greatest challenge.* Journal of the American College of Cardiology, 2008. **52**(23): p. 1817-1825.
47. Or, Z., F. Joust, and E. Yilmaz, *Impact of health care system on socioeconomic inequalities in doctor use*. 2008: Institut de recherche et documentation en économie de la santé.
48. Mullington, J.M., et al., *Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation.* Progress in cardiovascular diseases, 2009. **51**(4): p. 294-302.
49. Moore, P.J., et al., *Socioeconomic status and health: the role of sleep.* Psychosomatic medicine, 2002. **64**(2): p. 337-344.
50. Li, X., K. Sundquist, and J. Sundquist, *Socioeconomic status and occupation as risk factors for obstructive sleep apnea in Sweden: a population-based study.* Sleep medicine, 2008. **9**(2): p. 129-136.
51. Punjabi, N.M., *The epidemiology of adult obstructive sleep apnea.* Proceedings of the American Thoracic Society, 2008. **5**(2): p. 136-143.
52. Reece, J.B., Urry, L.A, Cain, M.L. 1., Wasserman, S.A., Minorsky, P.V., Campbell, N.A., *Campbell Biology*. Tenth edition ed. 2014, Boston.
53. Soltani, H., N. Keim, and K. Laugero, *Diet Quality for Sodium and Vegetables Mediate Effects of Whole Food Diets on 8-Week Changes in Stress Load.* Nutrients, 2018. **10**(11): p. 1606.
54. Fraga, S., et al., *Association of socioeconomic status with inflammatory markers: a two cohort comparison.* Preventive medicine, 2015. **71**: p. 12-19.
55. Ross, R., *Atherosclerosis—an inflammatory disease.* New England journal of medicine, 1999. **340**(2): p. 115-126.
56. Hansson, G.K., *Inflammation, atherosclerosis, and coronary artery disease.* New England Journal of Medicine, 2005. **352**(16): p. 1685-1695.
57. Doi, Y., et al., *Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: the Hisayama Study.* Diabetes care, 2005. **28**(10): p. 2497-2500.
58. Crimmins, E.M., et al., *Age differences in allostatic load: an index of physiological dysregulation.* Exp Gerontol, 2003. **38**(7): p. 731-4.
59. McEwen, B.S., *Stress, adaptation, and disease. Allostasis and allostatic load.* Ann N Y Acad Sci, 1998. **840**: p. 33-44.
60. McEwen, B.S. and T. Seeman, *Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load.* Annals of the New York Academy of Sciences, 1999. **896**(1): p. 30-47.
61. Gruenewald, T.L., et al., *History of socioeconomic disadvantage and allostatic load in later life.* Soc Sci Med, 2012. **74**(1): p. 75-83.
62. Dowd, J.B., A.M. Simanek, and A.E. Aiello, *Socio-economic status, cortisol and allostatic load: a review of the literature.* Int J Epidemiol, 2009. **38**(5): p. 1297-309.
63. Meaney, M.J., M. Szyf, and J.R. Seckl, *Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health.* Trends in molecular medicine, 2007. **13**(7): p. 269-277.
64. Hertzman, C. and T. Boyce, *How experience gets under the skin to create gradients in developmental health.* Annual review of public health, 2010. **31**: p. 329-347.
65. Stringhini, S., et al., *Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study.* 2012.

Chapter 1 The contribution of health behaviors to socioeconomic inequalities in health: A systematic review

Preventive Medicine 113 (2018) 15–31

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Review Article

The contribution of health behaviors to socioeconomic inequalities in health: A systematic review

Dusan Petrovic[a,*], Carlos de Mestral[a], Murielle Bochud[a], Mel Bartley[b], Mika Kivimäki[b], Paolo Vineis[c], Johan Mackenbach[d], Silvia Stringhini[a]

[a] Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Route de la corniche 10, 1010 Lausanne, Switzerland
[b] University College London (UCL), 536, 1-19 Torrington Place, WC1E 7HB London, United Kingdom
[c] Imperial College London, 511, Medical School, St Mary's Campus, London, United Kingdom
[d] Erasmus MC, Department of Public Health, P.O. Box 2040, 3000, CA, Rotterdam, The Netherlands

ARTICLE INFO

Keywords:
Socioeconomic position
Health behaviors
Contribution
All-cause mortality
Cardiometabolic disorders

ABSTRACT

Unhealthy behaviors and their social patterning have been frequently proposed as factors mediating socioeconomic differences in health. However, a clear quantification of the contribution of health behaviors to the socioeconomic gradient in health is lacking. This study systematically reviews the role of health behaviors in explaining socioeconomic inequalities in health.

Published studies were identified by a systematic review of PubMed, Embase and Web-of-Science. Four health behaviors were considered: smoking, alcohol consumption, physical activity and diet. We restricted health outcomes to cardiometabolic disorders and mortality. To allow comparison between studies, the contribution of health behaviors, or the part of the socioeconomic gradient in health that is explained by health behaviors, was recalculated in all studies according to the absolute scale difference method.

We identified 114 articles on socioeconomic position, health behaviors and cardiometabolic disorders or mortality from electronic databases and articles reference lists. Lower socioeconomic position was associated with an increased risk of all-cause mortality and cardiometabolic disorders, this gradient was explained by health behaviors to varying degrees (minimum contribution −43%; maximum contribution 261%).

Health behaviors explained a larger proportion of the SEP-health gradient in studies conducted in North America and Northern Europe, in studies examining all-cause mortality and cardiovascular disease, among men, in younger individuals, and in longitudinal studies, when compared to other settings. Of the four behaviors examined, smoking contributed the most to social inequalities in health, with a median contribution of 19%.

Health behaviors contribute to the socioeconomic gradient in cardiometabolic disease and mortality, but this contribution varies according to population and study characteristics. Nevertheless, our results should encourage the implementation of interventions targeting health behaviors, as they may reduce socioeconomic inequalities in health and increase population health.

1. Introduction

The existence of a stepwise association between socioeconomic position (SEP) and health related outcomes (Antonovsky, 1967; Krieger et al., 1997; Miranda et al., 2008; Bartley, 2004), also referred as the socioeconomic gradient in health, constitutes one of the most consistent findings of epidemiologic research. Individuals with a lower socioeconomic position, as measured by occupational position, educational attainment, income, or composite indexes, are more likely to die earlier and have a higher incidence of cardiovascular events, diabetes, obesity, and other diseases than their more advantaged counterparts (Bartley, 2004; Adler et al., 1993). As eliminating socioeconomic disadvantage from society is difficult, quantifying modifiable intermediate factors and targeting them could have important public health benefits. Epidemiologic research has long investigated potential mediating factors of the association between socioeconomic position and health outcomes, with health behaviors, environmental exposures or psychosocial factors having been identified as major mechanisms in the link between low SEP and increased disease risk (Supplementary Fig. 1) (Matthews et al., 2010; Stringhini et al., 2011a; Stringhini et al., 2012a; Robertson et al., 2015a; Næss et al., 2007; van Oort et al., 2005).

Health behaviors such as smoking, alcohol consumption, diet and

* Corresponding author.
E-mail address: dusan.petrovic@chuv.ch (D. Petrovic).

https://doi.org/10.1016/j.ypmed.2018.05.003
Received 20 October 2017; Received in revised form 2 May 2018; Accepted 5 May 2018
Available online 09 May 2018
0091-7435/

physical activity (PA) are major risk or protective factors for chronic diseases (Who and Consultation, 2003; Centers for Disease C, Prevention, 2008; Klatsky et al., 1992) and are also strongly socially patterned, with detrimental behaviors being more prevalent in lower SEP groups when compared to higher SEP groups (Nocon et al., 2007; Macintyre, 2000; Wardle and Steptoe, 2003). Yet, despite extensive investigations, a clear understanding of the role of health behaviors in social inequalities in health is still lacking, a major challenge being that their estimated contribution to the socioeconomic gradient in health varies greatly across studies, ranging from 12% to 72% (van Oort et al., 2005; Stringhini et al., 2011b; Laaksonen et al., 2008; Lantz et al., 1998; Schrijvers et al., 1999; Skalická et al., 2009; Stringhini et al., 2010).

The reasons for the differential contribution of health behaviors to social inequalities in health are numerous and include cultural differences between countries (Stringhini et al., 2011b), demographic characteristics of the participants included in the studies (Tseng and Lin, 2008), between-studies differences in the SEP measures, health behaviors and health outcomes examined, and methodological differences in the calculation of the contribution of health behaviors (Stringhini et al., 2010; Bartley, 2016). Another potential explanation may be related to the stage of the epidemiologic transition, which designates the changes in the prevalence of diseases, disease risk factors, and the changes in the adherence to health behaviors over time and in different sociodemographic contexts (Mackenbach et al., 1997). However, there is currently no attempt in the literature to synthesize the wealth of research on this topic and provide a more comprehensive assessment of health behaviors as mechanisms underlying the association between SEP and health. However, this is a crucial step for identifying targets for policies aimed at reducing socioeconomic differences in health as well as improving health at the population level.

In this study, we conducted a systematic review and synthesis of the literature on the contribution of smoking, alcohol intake, physical activity and dietary patterns to socioeconomic inequalities in all-cause mortality and risk of cardiometabolic disorders, two health outcomes showing a particularly consistent socioeconomic gradient across studies (Avendano et al., 2006a; Suadicani et al., 2001; Stringhini et al., 2013a; Mackenbach et al., 2008). The overarching purpose of this review was to examine all previously published studies investigating the contribution of health behaviors to socioeconomic inequalities in health, and to provide a complete and comprehensive analysis regarding the sources of heterogeneity of this contribution, with a particular focus on methodological, sociodemographic and cultural factors.

2. Methods

2.1. Search strategy and inclusion criteria

In this systematic review, we aimed to retrieve and analyze all articles that examined the contribution of health behaviors to the socioeconomic gradient in all-cause mortality and cardiometabolic disorders. We used four main groups of search terms: terms related to SEP, terms related to health behaviors, terms related to health outcomes, and terms related to "contribution", "role", or "mediation" (Supplementary Material – search strategy). Article search was performed from August 2015 to December 2016 by searching PubMed, Embase and Web-of-Science electronic databases following the PRISMA-Equity guidelines (Welch et al., 2012). No publication date restrictions were imposed. Articles in English and French were considered. Two reviewers (DP, CdM) independently examined the titles and abstracts of the papers identified in the databases search, removed papers that did not meet the inclusion criteria and selected eligible papers for full-text review. The reference lists of reviewed papers were also searched for additional articles of interest that were not identified by the electronic search.

In this review, we included four health behaviors that had been previously strongly related to SEP, but also to all-cause mortality and cardiometabolic disorders: smoking, alcohol consumption, physical activity, and dietary patterns (Who and Consultation, 2003; Centers for Disease C, Prevention, 2008; Klatsky et al., 1992; Jarvis and Wardle, 2005; Stringhini et al., 2013b; Trichopoulou and Lagiou, 1997; Mäki et al., 2014; Paffenbarger Jr et al., 1986). We also considered papers that performed analyses adjusted for multiple health behaviors simultaneously (i.e. smoking *and* alcohol). We searched for papers that reported SEP as measured by education, occupation, income, wealth, area-based indicators, childhood SEP indicators, partner's SEP as well as composite SEP scores (i.e. education and occupation). We included both cross-sectional and longitudinal observational studies investigating the contribution of the four health behaviors to socioeconomic inequalities in all-cause mortality and cardiometabolic outcomes (defined as cardiovascular disease, hypertension, coronary heart disease, stroke, diabetes, impaired glucose tolerance, metabolic syndrome, allostatic load, obesity). Despite the fact that some studies used BMI as a proxy for diet or a risk factor for other diseases, in the present review we considered it as a health outcome.

The main inclusion criterion in selected articles was the presence of a quantification of the contribution of health behaviors to the SEP gradient in health, or the possibility to estimate this from the data according to the difference method, which compares the coefficients from the SEP-health association model that is unadjusted for health behaviors, with the coefficients from a model additionally adjusted for health behaviors (Stringhini et al., 2010). Experimental studies (i.e. health education programs, randomized control trials), articles published in non-peer-reviewed journals, non-original research papers (i.e. reviews, commentaries), duplicate publications and articles limited to an abstract (i.e. congress proceedings) were excluded. After removing non-eligible papers, CdM and DP examined the papers to be included in the systematic review. For the title and abstract screening process, the level of agreement between the two reviewers was > 90%, while for full-text screening, the level of agreement between the two reviewers was > 95%. Whenever a conflict was encountered, the two reviewers discussed the article in question to decide whether to include it or not.

2.2. Data extraction

For each study, the following data were extracted: title, last name of first author, study region or country, cohort name, study period, study design, sample size, characteristics of participants, SEP indicator(s) (exposure), health outcome(s) (outcome) and health behavior(s) (mediating factor) along with their measurement methods (i.e. self-administered questionnaires, medical records, death registries), and two regression coefficients for SEP (β, hazard ratio (HR), odds ratio (OR), risk ratio (RR)) with 95% confidence intervals (CI); the first coefficient from the unadjusted regression model: SEP → health outcome (Model 1), and the second coefficient from the regression model additionally adjusted for health behavior(s) or mediator(s): SEP → health behavior(s) → health outcome (Model 2).

While the majority of the included papers did not provide any direct assessment of the contribution of health behaviors to socioeconomic differences in all-cause mortality and risk of cardiometabolic disorders, in 31 studies this contribution was calculated according to the absolute (n = 13) (Stringhini et al., 2011a; Stringhini et al., 2010; Suadicani et al., 2001; Stamler et al., 2003; László et al., 2008; Marmot et al., 2008; Kavanagh et al., 2010; Hagger-Johnson et al., 2012; Stringhini et al., 2012b; Woodside et al., 2012; Giesinger et al., 2013; Stringhini et al., 2014; Stringhini et al., 2016) or relative scale difference methods (n = 18) (van Oort et al., 2005; Laaksonen et al., 2008; Schrijvers et al., 1999; Skalická et al., 2009; Lynch et al., 1996; Van Lenthe et al., 2002; Agardh et al., 2004; Strand and Tverdal, 2004; van Oort et al., 2004; Khang and Kim, 2005; Silva et al., 2008; Singh-Manoux et al., 2008; Khang et al., 2009; Beauchamp et al., 2010; Chapman et al., 2010; Nandi et al., 2014; Bihan et al., 2016; Bonaccio et al., 2016) which compare the beta coefficient for SEP from the unadjusted regression

model (Model 1) with the beta coefficient from the regression model additionally adjusted for health behaviors (Model 2). Nine studies provided a quantification of the contribution of health behaviors by using alternative methods, namely path analysis model (Chaix et al., 2010; Robertson et al., 2015b), likelihood-ratio test statistic (Floud et al., 2016), Sobel's mediation test (Seligman et al., 2012; Ni et al., 2013; Zhu et al., 2015) and the mediation method based on direct and indirect effects (Nordahl et al., 2014a; Nordahl et al., 2014b; Houle et al., 2016).

Out of the 114 papers included in this review, 111 papers provided the estimators for the unadjusted and the health behavior adjusted models allowing the implementation of the difference method, while three studies assessed the contribution of health behaviors with an alternative method, and did not provide adequate information regarding the unadjusted and the adjusted models (Supplementary Fig. 2) (Houle et al., 2016; Jeffery et al., 1991; Schulz et al., 2008). Despite limitations of the difference method for assessing the contribution of mediating factors in an association, including unmeasured confounding variables and interactions (VanderWeele, 2013) as well as the possibility of yielding counter-intuitive negative contributions by health behaviors, this is to date the only statistical procedure that allows computing contribution of mediators based on statistical coefficients (β, OR, HR or RR) without individual-level data. Consequently, to allow comparison between studies, we recalculated the contribution of health behaviors with the absolute scale difference method for 111 out of 114 studies:

$$\text{Contribution of health behaviors (\%)} = 100 \times (\beta_{\text{Model 1}} - \beta_{\text{Model 2:Model 1+health behavior(s)}}) / \beta_{\text{Model 1}}$$

where β = β regression coefficient or log (HR, OR, RR) of the least advantaged SEP group for studies that used highest SEP group as a reference (n = 105). For studies that used the lowest SEP group as a reference, β coefficients from the highest SEP group were used for computing the contribution of health behaviors (László et al., 2008; Bonaccio et al., 2016; Egeland et al., 2002; Osler et al., 2003; Silventoinen et al., 2005; Gorman and Sivaganesan, 2007; Prescott et al., 2007; Fu et al., 2011; Bradley Deere and Seth, 2016). To illustrate the computation of the contribution of health behaviors, we can consider an example taken from a study by Stringhini et al. (Table 4 – Whitehall II data) (Stringhini et al., 2011a). The HR coefficient from the unadjusted model for the association between occupation and all-cause mortality is: 1.62 95%CI[1.28–2.05]. In the model additionally adjusted for smoking, the HR for the association between occupational position and all-cause mortality is 1.39 95%CI[1.09–1.75]. The contribution of smoking to the association between occupational position and all-cause mortality, is then calculated as:

$$100 \times (\log(1.62) - \log(1.39)) / \log(1.62) = 32\%$$

This percentage means that smoking contributes to approximately one third of the association between occupational position and all-cause mortality.

To analyze whether the contribution of health behaviors to the socioeconomic gradient differed by study settings, the contribution estimates computed for each article were grouped according to three main SEP indicators; namely education and occupation, which are the two most commonly used indicators, thought to capture multiple dimensions of SEP, and “Other SEP indicators” which included the remaining SEP markers (Stringhini et al., 2010; Galobardes et al., 2006). The contribution figures were further aggregated according to health outcome, sex, geographic location, age group of study participants, type of study (longitudinal vs. cross-sectional) and assessment method of health behaviors (questionnaire vs. objective assessment methods). For each group of studies that presented the same SEP indicator and aggregating factor, a median, minimum and maximum contribution were computed.

2.3. Mediators, confounders, and moderators/modifiers of the SEP-health association

In addition to mediating factors, the studies included in this review also reported specific sets of confounding and/or modifying factors that may affect the SEP-health association. In order to avoid confusion between the terms mediator, confounders and modifier, we provide the following explanations regarding their respective effects. Health behaviors are usually considered as mediating factors of the SEP-health association as they are strongly socially patterned and are simultaneously major risk or protective factors for health-related outcomes (Stringhini et al., 2010; Stringhini et al., 2013b; Kuh et al., 2003). Consequently, they contribute to this association by being located on the assumed causal pathway between SEP (exposure) and health (outcome) (Kuh et al., 2003). In contrast to mediators, factors such as age, sex, or ethnicity are usually considered as confounders, as they influence the SEP-health association but are not located on the causal pathway. Confounders are generally conceptualized as pre-existing or tangential to the exposure and often distort the effect of exposure on the outcome (Kuh et al., 2003; VanderWeele and Shpitser, 2013). Finally, there may also be risk or protective factors referred to as moderators or modifiers, which modify the association between the exposure and the outcome, when the effect of the exposure differs across levels of the moderator/modifier (Kuh et al., 2014; Sharma et al., 1981).

3. Results

Our search strategy identified 855 potentially relevant articles, of which 740 were found in three electronic databases and 115 were retrieved from reference lists. The article selection process and flow-chart are presented in Supplementary Fig. 2. A total of 537 articles were rejected based on Title/Abstract screening. These studies were mostly health intervention programs, randomized controlled trials or other experimental studies, did not assess the association between SEP and a health outcome, did not include one of the health outcomes of interest or performed reversed analyses (health outcome as predictor of SEP). A total of 318 articles were selected for full text reading, of which 204 were excluded, the main reason for exclusion being that they did not provide an estimate of the contribution of health behaviors separate from major confounders such as sex, age and/or pre-existing diseases. Other articles excluded based on full text reading were either narrative reviews or commentaries and not original articles, or used SEP as an adjustment factor only. The selection process eventually yielded 114 articles that were included in the systematic review.

3.1. General characteristics

General characteristics of the papers included in this systematic review are summarized in Table 1. The included studies (39 cross-sectional; 75 longitudinal) took place between 1948 and 2016, and were mainly conducted in high-income countries (United States (n = 27), United Kingdom (n = 23) and other countries from the Organization for Economic Co-operation and Development (n = 57) (Bank W, 2016)). Four studies took place in low or middle income countries, namely Kenya, Seychelles and China, and three were international consortia. In 113 articles, analyses were carried out in adults, of which 13 also included adolescents. One article reported analyses performed in individuals aged 8–19 (Schreier and Chen, 2010). In 27 articles, analyses were stratified by sex while ten studies included men only and ten women only. To assess the association between SEP and health outcomes, most studies relied on logistic or Cox proportional hazards regression models, whereas others used linear or non-linear (Poisson) regression models.

Table 1
General characteristics of the studies included in the systematic review.

Study	Country	Survey period	Study/cohort name	Type of study	Age at baseline	Number included	SEP indicator(s)	Outcome(s)	Lifestyle behavior(s)
Notkola et al. (1985)	Finland	1959–1974	East-West study	Longitudinal	40–60+	1711	Childhood SES (OA)	CVD (OA)	Smoking (Q)
Jacobsen and Thelle (1988)	Norway	1980	The Tromso Heart Study	Cross-sectional	25–55	11,562	Education (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Jeffery et al. (1991)	US	< 1991	Healthy Worker Project	Cross-sectional	38.7 (mean age)	4647	SES score (Q)	Obesity (OA)	Smoking, PA, diet (Q)
Stamler et al. (1992)	International	1982–1985	Intersalt Study	Cross-sectional	20–59	8477	Education (Q)	CVD (OA)	Alcohol, smoking, diet (Q)
Helmert and Shea (1994)	Germany	1984–1991	German Cardiovascular Prevention Study	Cross-sectional	25–69	44,363	SES score (Q)	Diabetes, CVD (OA)	Smoking (Q)
Gliksman et al. (1995)	US	1976–1990	Nurses' Health Study Cohort	Longitudinal	30–55	117,006	Childhood SES (Q)	CVD (OA)	Alcohol, PA, diet (Q)
Pekkanen et al. (1995)	Finland	1972–1987	North Karelia Project	Longitudinal	25–59	18,661	Occupation (Q)	ACM, CVD (OA)	Smoking (Q)
Brancati et al. (1996)	US	1972–1974	Three Area Stroke Study	Cross-sectional	35–54	1393	SES score (Q)	Diabetes (OA)	Smoking (Q)
Lynch et al. (1996)	Finland	1984–1993	Kuopio Ischemic Heart Disease Risk Factor Study	Longitudinal	42–90	2682	Income (Q)	ACM, CVD (OA)	Alcohol, smoking, PA (Q)
Suadicani et al. (1997)	Denmark	1985–1991	Copenhagen Male Study	Longitudinal	53–75	2974	Occupation (Q)	CVD (Q + OA)	Alcohol, PA, diet (Q)
Wannamethee and Shaper (1997)	UK	1983–1995	British Regional Heart Study	Longitudinal	40–59	7262	Occupation (RGC)	ACM, CVD (OA)	Smoking (Q)
Chandola (1998)	UK	1984–1995	The Health Lifestyles Survey	Longitudinal	≥18	9003	Occupation (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Lantz et al. (1998)	US	1986–1994	Americans' Changing Live's Survey	Longitudinal	≥25	3617	Education, income (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Schrijvers et al. (1999)	Netherlands	1991–1996	Longitudinal Study on Socioeconomic Health Differences	Longitudinal	15–74	15,451	Education (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Hart et al. (2000)	UK	1972–1976	Renfrew/Praisley General Population Study	Longitudinal	45–64	14,947	Occupation, wealth (RGC)	CVD (OA)	Smoking (Q)
Kilander et al. (2001)	Sweden	1970–1995	Uppsala Male Health Survey	Longitudinal	50	2301	Education (Q)	CVD (OA)	Smoking (Q)
Suadicani et al. (2001)	Denmark	1971–1993	Copenhagen Male Study	Longitudinal	40–59	5028	SES score (Q)	CVD (OA)	Alcohol, smoking, PA (Q)
Egeland et al. (2002)	Norway	1977–1992	Second Cardiovascular Disease and Risk Factor Screening Survey	Longitudinal	35–52	20,038	Education, Partner's SES (Q)	CVD (OA)	Smoking (Q)
Van Lenthe et al. (2002)	Netherlands	1991–1996	Globe Study	Longitudinal	15–74	9872	Education (Q)	CVD (OA)	Alcohol, smoking, PA (Q)
Aslanyan et al. (2003)	UK	1991–1998	Stroke Patients admitted to the Western Infirmary Acute Stroke Unit in Glasgow	Cross-sectional	≥18	2026	Area SES (OA)	CVD (OA)	Smoking (Q)
Osler et al. (2003)	Denmark	1980–1997	Copenhagen City Heart Study	Longitudinal	≥20	21,721	Income, area SES (OA)	CVD (OA)	Alcohol, smoking, PA (Q)
Stamler et al. (2003)	US	1992	Intermap Study	Cross-sectional	40–59	2195	Education (Q)	CVD (OA)	Alcohol, diet (Q)
Woodward et al. (2003)	UK	1984–1993	Scottish Heart Health Study	Longitudinal	40–59	11,629	Wealth (Q)	CVD (OA)	Alcohol, smoking, PA (Q + OA)
Agardh et al. (2004)	Sweden	1992–1998	Stockholm Diabetes Prevention Program	Cross-sectional	35–56	7949	Occupation (Q)	Diabetes (OA)	Smoking, PA (Q)
Lawlor et al. (2004)	UK	1999–2001	British Women's Heart and Health Study	Cross-sectional	60–79	3444	Childhood SES (RGC)	CVD (OA)	Smoking, PA (Q)
Strand and Tverdal (2004)	Norway	1974–2000	Cardiovascular Disease Study in Finnmark, Sogn og Fjordan, Oppland	Longitudinal	35–74	44,144	Education (Q)	CVD (OA)	Smoking, PA (Q)
van Oort et al. (2004)	Netherlands	1991–1998	Globe Study	Longitudinal	15–74	16,980	Education (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Blakely and Wilson (2005)	New Zealand	1981–1984 1996–1999	New Zealand Census Mortality Study	Longitudinal	45–74	1,175,000	Education (Q)	ACM, CVD (OA)	Smoking (Q)

(continued on next page)

Table 1 (*continued*)

Study	Country	Survey period	Study/cohort name	Type of study	Age at baseline	Number included	SEP indicator(s)	Outcome(s)	Lifestyle behavior(s)
Khang and Kim (2005)	South Korea	1998	KNHANES Study	Cross-sectional	≥30	5437	Income (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Maty et al. (2005)	US	1965–1999	Alameda County Study	Longitudinal	17–94	6147	Education, occupation, income (Q)	Diabetes (Q)	Alcohol, smoking, PA (Q)
Power et al. (2005)	UK	1958–1991	British Birth Cohort	Longitudinal	14–49	11,855	Partner's SES, childhood SES (RGC)	ACM (OA)	Smoking (Q)
Silventoinen et al. (2005)	Finland	1992–2001		Longitudinal	25–64	1909	Education (Q)	CVD, MS (OA)	Alcohol, smoking, PA, diet (Q)
van Oort et al. (2005)	Netherlands	1991–1998	Globe Study	Longitudinal	15–74	3979	Education (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Avendano et al. (2006b)	US	1982–1994	Epese Study	Longitudinal	65–74	2812	Education, income (Q)	CVD (Q + OA)	Alcohol, smoking, PA (Q)
Kittleson et al. (2006)	US doctors (all age groups)	1948–1988	Johns Hopkins Precursors Study	Longitudinal	26–70	1131	Childhood SES (Q)	CVD (OA)	Smoking, PA (Q)
Kittleson et al. (2006)	US (< 50 y of age)	1948–1988	Johns Hopkins Precursors Study	Longitudinal	26–50	< 1131	Childhood SES (Q)	CVD (OA)	Smoking, PA (Q)
Rathmann et al. (2006)	Germany	1999	KORA survey 2000	Cross-sectional	55–74	1476	SES score (Q)	Diabetes (OA)	Smoking, PA (Q)
Yan et al. (2006)	US	1985–2001	Coronary Artery Risk Development in Young Adults study	Longitudinal	18–30	2913	Education (Q)	CVD (OA)	Smoking, PA (Q)
Agardh et al. (2007)	Sweden	1992–1998	Stockholm Diabetes Prevention Program	Cross-sectional	35–56	7949	Education, occupation, childhood SES (Q)	Diabetes (OA)	Smoking, PA (Q)
Feinglass et al. (2007)	US	1992–2002	Health and Retirement Study	Longitudinal	51–61	9759	Education, income, wealth (Q)	ACM (OA)	Smoking, PA (Q)
Gorman and Sivaganesan (2007)	US	2001	National Health Interview Survey	Cross-sectional	≥25	29,767	Education, wealth (Q)	CVD (Q)	Alcohol, smoking, PA (Q)
Kivimäki et al. (2007)	Finland	2000–2002	The Finnish Public Sector Study	Cross-sectional	17–65	48,592	Income (OA)	CVD (Q)	Alcohol, smoking, PA (Q)
Kuper et al. (2007)	Sweden	1991–2002	Women's Lifestyle and Health Cohort Study	Longitudinal	30–50	47,942	Education (Q)	CVD (OA)	Alcohol, smoking, PA (Q)
Loucks et al. (2007)	US	1988–1994	NHANES III	Cross-sectional	≥25	11,107	Education, wealth (Q)	MS (OA)	Alcohol, smoking, PA, diet (Q)
Prescott et al. (2007)	Denmark	1976–2003	Copenhagen Swiss National Science Foundation	Cross-sectional	≥20	6069	Education (Q)	MS (OA)	Alcohol, smoking, PA (Q)
Ito S et al., 2008 (Ito et al., 2008)	Japan	1990–2003	Japan Public Health Center-based Prospective Study	Longitudinal	40–59	39,228	Education (Q)	ACM, CVD (OA)	Alcohol, smoking, PA, diet (Q)
Laaksonen et al. (2008)	Finland	1979–2001	Finnish Health Behaviors Survey and Finnish National Causes of Death Register	Longitudinal	25–64	60,000	Education (Q)	ACM, CVD (OA)	Alcohol, smoking, PA, diet (Q)
László et al. (2008)	Sweden	1996–2000		Longitudinal	< 75	188	Income (Q)	CVD (OA)	Alcohol, smoking (Q)
Marmot et al. (2008)	UK	1985–2004	Whitehall II	Longitudinal	35–55	5312	Occupation (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Maty et al. (2008)	US	1965–1999	Alameda County Study	Longitudinal	17–94	5913	Education, occupation, income, childhood SES (Q)	Diabetes (Q)	Alcohol, smoking, PA (Q)
McFadden et al. (2008)	UK	1993–2006	EPIC-Norfolk Cohort	Longitudinal	39–79	22,486	Occupation (RGC)	ACM, CVD (OA)	Smoking (Q)
Panagiotakos et al. (2008)	Greece	2001–2005	Attica Study	Longitudinal	≥18	3042	Education (Q)	CVD (OA)	Alcohol, diet (Q)
Ramsay et al. (2008)	UK	1978–2000	British Regional Heart Study	Cross-sectional	60–79	2968	Occupation, childhood SES (RGC)	MS (OA)	Alcohol, smoking, PA (Q)
Schulz et al. (2008)	US	2002	Healthy Environments Partnership Community Survey	Cross-sectional	≥25	919	Education, income (Q)	Obesity (OA)	Alcohol, PA (Q)
Silva et al. (2008)	Netherlands	2002–2006	Generation R Study	Cross-sectional	30–35	9778	Education (Q)	CVD (OA)	Alcohol, smoking (Q)
Singh-Manoux et al. (2008)	UK	1985–2004	Whitehall II	Longitudinal	35–55	5363	Occupation (OA)	CVD (OA)	Smoking (Q)
Khang et al. (2009)	South Korea	1998–2001	Korea National Health and Nutrition Examination Survey (KNHANES)	Longitudinal	≥30	8366	Education, occupation (Q)	ACM (OA)	Alcohol, smoking, PA (Q)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Survey period	Study/cohort name	Type of study	Age at baseline	Number included	SEP indicator(s)	Outcome(s)	Lifestyle behavior(s)
McFadden et al. (2009)	UK	1993–1997	Norfolk Cohort	Longitudinal	39–79	22,488	Occupation (RGC)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Münster et al. (2009)	Germany	2006–2007	German National Telephone Health Interview Survey and OI-Survey	Cross-sectional	≥40	9267	Wealth (Q)	Obesity (Q)	Smoking (Q)
Rosengren et al. (2009)	International	1999–2003	Interheart study	Longitudinal	≥18	27,098	Education, occupation, income, wealth (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Rostad et al. (2009)	Norway	1995–2007	The HUNT Study	Longitudinal	≥70	5607	Education (Q)	ACM, CVD (OA)	Smoking, PA (Q)
Skalická et al. (2009)	Norway	1995–1997	Hunt Study	Longitudinal	24–80	36,525	Education, income (OA)	ACM (OA)	Alcohol, smoking, PA (Q)
Beauchamp et al. (2010)	Australia	1991–1994	Melbourne Collaborative Cohort Study	Longitudinal	40–69	38,355	Education (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Chaix et al. (2010)	France	2007–2008		Cross-sectional	30–79	5941	Education, area SES (OA)	CVD (OA)	Alcohol, smoking (Q)
Chapman et al. (2010)	US	1995–2005	Midlife Development in the United States Study	Longitudinal	25–74	2998	SES score (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Kavanagh et al. (2010)	Australia	1999–2000	AusDiab Study	Cross-sectional	25–64	8866	Education, income (Q)	Diabetes, CVD (OA)	Alcohol, smoking, PA, diet (Q)
Krishnan et al. (2010)	US	1995–2007	Black Women's Health Study	Longitudinal	30–69	46,382	Education, income, area SES (OA)	Diabetes (OA)	Alcohol, smoking, PA (Q)
Lantz et al. (2010)	US	1986–2005	Americans' Changing Live's Survey	Longitudinal	≥25	3617	Education, income (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Manuck et al. (2010)	US	2001–2005	Adult Health and Behavior Registry	Cross-sectional	30–54	981	SES score (Q)	MS (OA)	Smoking, PA (Q)
Maty et al. (2010)	US White	1965–1995	Alameda County Study	Longitudinal	20–94	4774	Education, occupation, income, childhood SES (Q)	Diabetes (Q)	Alcohol, smoking, PA (Q)
Maty et al. (2010)	US Black	1965–1995	Alameda County Study	Longitudinal	20–94	4774	Education, occupation, income, childhood SES (Q)	Diabetes (Q)	Alcohol, smoking, PA (Q)
Schreier and Chen (2010)	Canada	2008		Cross-sectional	8–19	88	Childhood SES (Q)	CVD (OA)	Smoking, PA (Q)
Steptoe et al. (2010)	UK	2006–2008	Whitehall II Study	Cross-sectional	53–76	528	Occupation (OA)	CVD (OA)	Alcohol, smoking, PA (Q)
Stringhini et al. (2010)	UK	1985–2009	Whitehall II Study	Longitudinal	35–55	10,308	Occupation (OA)	ACM, CVD (OA)	Alcohol, smoking, PA, diet (Q)
Williams et al. (2010)	Australia	1999–2005	AusDiab Study	Longitudinal	≥25	4405	Education (Q)	Diabetes (OA)	Smoking, PA (Q)
Brummett B.H. et al., 2011 (Brummett et al., 2011)	US	1995–2008	National Longitudinal Study of Adolescent Health	Longitudinal	28–30	14,299	Education, income, childhood SES (Q)	CVD (OA)	Alcohol, smoking, PA (Q)
Demakakos et al. (2012)	UK	1998–2003	ELSA	Longitudinal	≥50	7432	Education, occupation, income, wealth, childhood SES (Q)	Diabetes (OA)	Alcohol, smoking, PA (Q)
Dinca-Panaitescu et al. (2011)	Canada	2005	Canadian Community Health Survey	Cross-sectional	≥12	98,298	Education, income (Q)	Diabetes (Q)	PA (Q)
Franks et al. (2011)	US	1987–1997	Atherosclerosis Risk in Communities Study	Longitudinal	45–64	15,495	SES score (Q)	CVD (OA)	Smoking (Q)
Fu et al. (2011)	China	2006–2007	Rural Deqing Cohort Study	Cross-sectional	18–64	5898	Education, occupation, income (Q)	Diabetes (OA)	Alcohol, smoking, PA (Q)
Gustafsson et al. (2011)	Sweden	1983–2008	Northern Swedish Cohort	Longitudinal	16	832	SES score (Q)	MS (OA)	Alcohol, smoking, PA (Q)
Niedhammer et al. (2011)	France	1996–2008	Lorhandicap Study	Longitudinal	≥15	4118	Occupation (Q)	ACM (OA)	Alcohol, smoking (Q)
Silhol et al. (2011)	France	1990–2000	Gazel Cohort	Longitudinal	35–55	19,808	Education, occupation, income, area SES (Q)	CVD (OA)	Smoking, diet (Q)
Stringhini et al. (2011a)	UK-Whitehall	1985–2005	Whitehall II Study	Longitudinal	35–55	9771	Education, occupation, income (OA)	ACM (OA)	Alcohol, smoking, PA, diet (Q)
Stringhini et al. (2011a)	France-Gazel	1985–2005	Gazel Cohort	Longitudinal	35–50	17,760	Education, occupation, income (OA)	ACM (OA)	Alcohol, smoking, PA, diet (Q)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Survey period	Study/cohort name	Type of study	Age at baseline	Number included	SEP indicator(s)	Outcome(s)	Lifestyle behavior(s)
Dinca-Panaitescu et al. (2012)	Canada	1994–2007	Canada's National Population Health Survey	Longitudinal	≥12	17,276	Income (Q)	Diabetes (Q)	PA (Q)
Hagger-Johnson et al. (2012)	UK	1984–2009		Longitudinal	35–75	5450	SES score (RGC)	ACM (OA)	Alcohol, smoking, PA, diet (Q)
Ploubidis et al. (2013)	Kenya - urban population	2007–2008	Nakuru Population-Based Survey	Cross-sectional	≥50	4314	Education, wealth (Q)	Diabetes, CVD (Q + OA)	Alcohol, smoking (Q)
Ploubidis et al. (2013)	Kenya - rural population	2007–2008	Nakuru Population-Based Survey	Cross-sectional	≥50	4314	Education, wealth (Q)	Diabetes, CVD (Q + OA)	Alcohol, smoking (Q)
Seligman et al. (2012)	US	2008–2009	Immigration, Culture and Healthcare Study	Cross-sectional	≥18	711	Wealth (OA)	Diabetes (OA)	Diet (Q)
Stringhini et al. (2012a)	UK	1991–2009	Whitehall II	Longitudinal	35–55	7237	Occupation (OA)	Diabetes (OA)	Alcohol, smoking, PA, diet (Q)
Tanaka et al. (2012)	UK	2004–2008	English Longitudinal Study of Ageing	Longitudinal	≥50	9432	Income, wealth (Q)	Diabetes, obesity (Q + OA)	Alcohol, smoking, PA (Q)
Williams et al. (2012)	Australia	1999–2004	AusDiab Study	Longitudinal	≥25	4572	Area SES (OA)	Diabetes (OA)	Alcohol, smoking, PA, diet (Q)
Woodside et al. (2012)	France and UK	1991–2004	Prime Study	Longitudinal	50–59	10,600	Education, wealth (Q)	ACM, CVD (OA)	Alcohol, PA, diet (Q)
Ni et al. (2013)	Taiwan	2002	Taiwanese Survey on Prevalence of Hypertension, Hyperglycemia and Hyperlipidemia	Cross-sectional	18–94	6188	SES score (Q)	MS (OA)	Alcohol, smoking (Q)
Shamshirgaran et al. (2013)	Australia	2006–2009	45 and Up Study	Cross-sectional	≥45	266,848	Education, income, wealth (Q)	Diabetes (Q)	Smoking, PA (Q)
Dinwiddie et al. (2014)	US - foreign born US Mexicans	2001–2008	National Health and Nutrition Examination Survey	Cross-sectional	≥20	6032	Education (Q)	Diabetes, CVD, obesity (OA)	Alcohol, smoking, PA (Q)
Dinwiddie et al. (2014)	US - US born US Mexicans	2001–2008	National Health and Nutrition Examination Survey	Cross-sectional	≥20	6032	Education (Q)	Diabetes, CVD, obesity (OA)	Alcohol, smoking, PA (Q)
Giesinger et al. (2013)	UK	1971–2002	1946 Birth Cohort	Longitudinal	26	2132	Childhood SES (RGC)	ACM (OA)	Smoking (Q)
Hwang and Shon (2014)	South Korea	2010–2012	Korea National Health and Nutrition Examination Survey (KNHANES)	Cross-sectional	30–65+	14,330	Education, income, wealth (Q)	Diabetes (Q + OA)	Alcohol, smoking, PA (Q)
Lear et al. (2014)	International	2002–2009	Prospective Urban Rural Epidemiology Study	Cross-sectional	35–70	139,000	Wealth (Q)	Diabetes, obesity (Q + OA)	PA (Q)
Lipowicz et al. (2014)	Poland	1983–1993	Lower Silesian Centre for Preventive Medicine Health Survey	Cross-sectional	25–60	3887	Education (Q)	MS (OA)	Alcohol, smoking, PA (Q)
Nandi et al. (2014)	US	1992; 1998–2008	Health and Retirement Study	Longitudinal	57–67	8037	Education, occupation, income, wealth, SES score, childhood SES (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Nordahl et al. (2014a)	Denmark	1981–2009		Longitudinal	≥18	69,513	Education (Q)	CVD (OA)	Smoking, PA (Q)
Nordahl et al. (2014b)	Denmark	Differs-2009	Social Inequality in Cancer Cohort Study	Longitudinal	30–70	76,294	Education (Q)	ACM, CVD (OA)	Smoking (Q)
Stringhini et al. (2014)	Seychelles	1989–1994–2004-(2012)	Seychelles Study	Longitudinal	25–64	3246	Occupation (Q)	ACM (OA)	Alcohol, smoking (Q)
Tamayo et al. (2014)	Germany	2006–2008	Heinz Nixdorf Recall Study	Cross-sectional	67.2 ± 7.3	662	Education, income, wealth (Q)	Diabetes (Q)	Alcohol, smoking, PA (Q)
Dupre et al. (2015)	US elderly (low Hba1c)	2006–2008	Health and Retirement Study	Longitudinal	65–75	3312	Education (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Dupre et al. (2015)	US elderly (high Hba1c)	2006–2008	Health and Retirement Study	Longitudinal	65–75	3312	Education (Q)	ACM (OA)	Alcohol, smoking, PA (Q)
Panagiotakos et al. (2015)	Greece	2001–2002	Attica Study	Longitudinal	18–89	2020	Education (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Robertson et al. (2015b)	UK	1987–2008	West of Scotland Twenty-07 Study	Longitudinal	35	1444	Occupation (RGC)	MS (OA)	Alcohol, smoking, PA, diet (Q)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Survey period	Study/cohort name	Type of study	Age at baseline	Number included	SEP indicator(s)	Outcome(s)	Lifestyle behavior(s)
Zhu et al. (2015)	China	2013		Cross-sectional	35–76	3243	Occupation, income (Q)	Diabetes (OA)	Alcohol, smoking, PA, diet (Q)
Bihan et al. (2016)	Australia	1999–2012	AusDiab Cohort	Longitudinal	≥25	9338	Education, area SES (Q + OA)	ACM (OA)	Smoking, PA, diet (Q)
Bonaccio et al. (2016)	Italy	2005–2010	MOLI-SANI	Longitudinal	≥35	16,247	SES score (Q)	ACM (OA)	Smoking, PA, diet (Q)
Bradley Deere and Seth (2016)	US	2000–2008	Jackson Heart Study	Cross-sectional	21–95	3114	Education, income, childhood SES (Q)	CVD (OA)	Alcohol, smoking, PA, diet (Q)
Floud et al. (2016)	UK	1996–2011	Million Women Study	Longitudinal	44–68	1,202,983	Education, area SES (Q)	CVD (OA)	Alcohol, smoking, PA (Q)
Houle et al. (2016)	Canada	2016		Cross-sectional	31–83	284	Education, childhood SES (Q)	Diabetes (OA)	Diet (Q)
Montez et al. (2016)	US	1996–2013	Study of Women's Health Across the Nation	Longitudinal	42–52	826	Education, childhood SES (Q)	MS (OA)	Alcohol, smoking, PA (Q)
Montez et al. (2016)	US	1996–2013	Study of Women's Health Across the Nation	Cross-sectional	42–52	826	Education, childhood SES (Q)	MS (OA)	Alcohol, smoking, PA (Q)
Poulsen and Andersen, 2016	Denmark	1995–2005	Danish Work Environment Cohort Study	Longitudinal	30–59	6823	Occupation (Q)	Diabetes (OA)	Smoking (Q)
Stringhini et al. (2016)	UK	2004–2013	ELSA	Longitudinal	≥50	6218	Education, wealth, SES score, childhood SES (Q)	Diabetes (OA)	Alcohol, smoking, PA (Q)

ACM: All-cause mortality, CVD: Cardiovascular disease (including mortality, incidence, morbidity, prevalence, stroke, coronary heart disease), MS: Metabolic syndrome (including allostatic load), PA: Physical activity. Assessment methods: Q: Self-administered questionnaire, Qa: Questionnaire adjusted according to validated methods (FFQ); OA: Objective assessment (death registries, medical records, accelerometer for measure of physical activity,…), RGC: Registrar's general classification based on occupation.

3.2. SEP indicators

In two thirds of the included studies (n = 72), only one SEP indicator was used, while 42 studies used more than one indicator. 89 articles used self-administered questionnaires to measure SEP, while 25 relied on more objective methods including work registries or adjusted questionnaires according to validated methods (i.e. Registrar general's classification based on occupation (Hagger-Johnson et al., 2012; Giesinger et al., 2013; McFadden et al., 2008)). The main SEP indicator was participant's education (n = 63), followed by income (n = 31) and occupation (n = 30). Alternative indicators were also used, such as wealth or poverty levels (n = 18), partner's education or occupation (n = 2), area based indicators (n = 8) as well as composite SEP scores (n = 14) which were computed based on several SEP indicators (i.e. education and occupation). Other studies assessed childhood SEP indicators, such as parental education, occupation or living conditions in childhood.

3.3. Health outcomes

The majority of studies included only one health outcome (n = 96), 17 studies examined two health outcomes and, one study assessed three outcomes. Generally, health outcomes were assessed through objective measures including death registries or medical records (n = 98). Most studies assessed cardiovascular diseases such as stroke, coronary heart disease or hypertension (n = 57) and all-cause mortality (n = 31). A total of 29 studies assessed diabetes or impaired glucose tolerance, whereas obesity was used as an outcome in 6 studies, and composite health outcomes such as metabolic syndrome and allostatic load were assessed in 10 studies.

3.4. Health behaviors

Generally, included studies assessed the contribution of several health behaviors (n = 96), whose information was almost exclusively collected through self-administered questionnaire (n = 113), except for one study that also assessed smoking according to cotinine levels in blood (Woodward et al., 2003). Smoking was the most common behavior assessed (n = 103), followed by physical activity (n = 83), alcohol consumption (n = 73) and dietary patterns (n = 31).

Table 2 shows the median contribution of multiple health behaviors to socioeconomic differences in all-cause mortality and cardiometabolic disorders, stratified by the type of SEP indicator, health outcomes, sex, study region, age groups, type of study and assessment method of health behaviors. Health behaviors generally contributed similarly to the SEP gradient in the health outcomes examined; the median contributions being between 20% and 26% for all-cause mortality, between 16% and 33% for cardiovascular disorders, and between 17% and 29% for metabolic disorders.

However, a generally higher contribution of health behaviors was observed in studies that used occupational position instead of other SEP indicators. Health behaviors generally contributed to a greater extent to the associations between SEP and health outcomes in Northern Europe, with **median contributions** varying between 29% and 36%, followed by the remaining regions (other OECD countries and other low and middle-income countries) (16% to 25%), North America (12% to 25%) and Central/Southern Europe with median contributions ranging between 10% to 18% (one outlier study with 64% contribution (Chaix et al., 2010)). Finally, median contributions tended to be higher in longitudinal studies (23% to 31%) when compared to cross-sectional studies (12% to 21%).

Table 3 presents the median contribution of smoking (Panel A) and alcohol consumption (Panel B) to socioeconomic differences in all-cause mortality and cardiometabolic disorders. The median contribution of smoking to the socioeconomic gradient was the highest for all-cause mortality (19% to 32%), followed by metabolic disorders (14% to

22%) and cardiovascular disease (15% to 17%). However, the median contribution varied according to SEP indicator, and was generally higher for occupation. Smoking contributed to the socioeconomic gradient slightly more in men (12% to 22%) than in women (6% to 19%), and more in Northern Europe (17% to 19%) and North America (2% to 35%), than in Central/Southern Europe (4%) or other regions (11% to 15%). The median contribution of smoking was also higher in studies with greater proportion of younger individuals, as well as in longitudinal studies than in cross-sectional ones. Alcohol's median contribution (Panel B) was higher for cardiovascular disorders (6% to 64%) than for all-cause mortality (−2% to 17%) or metabolic disorders (2%). While no particular difference was observed between men and women, the median contribution of alcohol tended to be higher and broader in North America (2% to 139%) than in other regions.

The contributions of physical activity (Panel A) and dietary patterns (Panel B) to socioeconomic differences in health are shown in Table 4. The median contribution of PA to the SEP-health gradient was higher for all-cause mortality (12% to 20%) and cardiovascular disorders (4% to 19%) than for metabolic disorders (6% to 9%), but varied in men and women according to the SEP indicator. Similarly to smoking and alcohol, the contribution of PA was higher for studies conducted in Northern Europe (6% to 13%) and North America (−2% to 26%) than in Central/Southern Europe (8%). Dietary patterns contributed more to the SEP gradient in all-cause mortality (17% to 21%) and cardiovascular disorders (7% to 24%) than in metabolic disorders (10% to 11%). Furthermore, the median contribution was higher in men (36%) than in women (11%). The contribution of dietary patterns was generally higher in Northern Europe (13% to 26%) and North America (11% to 29%) and for middle-aged individuals (13% to 27%) than for other regions or age groups.

4. Discussion

In this study, we reviewed the evidence on the contribution of smoking, alcohol consumption, physical activity and dietary patterns on social inequalities in all-cause mortality and cardiometabolic disorders. We confirmed the existence of a strong association between SEP and health outcomes, and showed that health behaviors contribute to the SEP gradient in health to varying degrees. In general, the contribution of health behaviors to socioeconomic differences in health was higher in studies conducted in North America and Northern Europe than in Central/Southern Europe, in men than in women, in younger and middle-aged individuals than in older individuals, for smoking when compared to other health behaviors, for all-cause mortality and cardiovascular disease than for metabolic disorders and in longitudinal studies compared to cross-sectional studies. Furthermore, we also observed that the contribution tended to be higher for the socioeconomic gradient in health when occupational position was used as the indicator of socioeconomic position. These findings are of particular interest when considering implementation of prevention policies, as future measures and interventions aiming to reduce the socioeconomic gradient in health could focus on health behaviors with the highest impact in given geographic and sociodemographic contexts (Mackenbach et al., 2008).

Health behaviors are plausible mediators of social inequalities in health as they are strongly socially patterned and simultaneously related to health outcomes (Who and Consultation, 2003; Centers for Disease C, Prevention, 2008; Macintyre, 2000; Doll and Hill, 1950). Previous research has shown that socially disadvantaged individuals tend to adhere more to health detrimental behaviors either due to material and financial constraints, perception of fewer benefits of health behaviors for longevity, a lack of knowledge of their detrimental effect, difficulties to take up health promoting messages as well as more pessimistic attitudes about life (Wardle and Steptoe, 2003; Stringhini et al., 2011b; Pampel et al., 2010). Previous studies have also shown that low SEP individuals lack the resources to buy adequate food or sports equipment (Laaksonen et al., 2003), or have no access to sports facilities, as safe areas or adequate transport may not be always available (Macintyre, 2000; Chinn et al., 1999). Furthermore, deprived neighborhoods frequently offer little opportunity for a healthy life (Walker et al., 2010). These areas are often characterized by an absence of supermarkets offering a variety of affordable and healthy foods but on the other hand are full of small convenience stores which sell highly-advertised tobacco, alcohol, processed foods (i.e. snacks, sodas) and no or few fruits and vegetables (Walker et al., 2010). An additional aspect concerns the motivations, beliefs and attitudes that socially disadvantaged individuals have towards health behaviors. For example, it has been shown that less advantaged SEP individuals tend to be less conscious about healthy behaviors, have stronger beliefs in the influence of chance over health and were generally more pessimistic or fatalistic about their life expectancy, altogether acting as an additional barrier to a healthy lifestyle (Wardle and Steptoe, 2003).

4.1. Social patterning of health behaviors

Our review confirms that health behaviors contribute to the socioeconomic gradient in health, yet the extent of this contribution varied greatly across included articles, the main reason being the differential social patterning of health behaviors, which designates an unequal distribution of health behaviors across socioeconomic groups in given socio-demographic, regional and cultural contexts (Stringhini et al., 2011b). The differential social patterning of health behaviors according to age, gender and region may be explained by the epidemiologic transition from the “diseases of affluence” towards the “diseases of the poor”. According to this model, coronary heart disease and related health behaviors such as smoking and an energy-dense diet were originally more prevalent in the higher socioeconomic groups, but their burden started to gradually shift to the lower SEP groups along with the progression of the epidemiologic transition (Marmot et al., 1978; Wilkinson, 1994). The epidemiologic transition progressed at a different pace in different geographical regions and for men and women, due to economic, social or cultural factors (Omran, 2005). In the same way, it is hypothesized that the socioeconomic gradient in chronic diseases and related health behaviors also reversed (from higher prevalence in the higher SEP groups to higher prevalence in the lower) at different times in different countries and for men than for women (Stringhini et al., 2011b). We have tested this hypothesis by stratifying the articles by periods during which the studies were conducted, and observed that the overall contribution of smoking to the socioeconomic gradient in health has increased over time (results available from the authors). These results are in line with the smoking epidemic model, which shows that smoking prevalence rates differ by gender and SEP in different stages of the epidemic (Lopez et al., 1994). These differences are likely due to socio-cultural factors such as the level of gender equality in the country, as smoking could be/has been perceived as a symbol of emancipation by women, especially in the higher socioeconomic groups at the early stages of the epidemics (Hitchman and Fong, 2011; Huisman et al., 2005). As regions such as Southern Europe are at later stages of the smoking epidemics, smoking may still be more common in women with higher education, likely due to the delayed acquisition of full social and political rights (Hitchman and Fong, 2011; Huisman et al., 2005; Curtin et al., 1997; Thun et al., 2012). The succession of different stages of the smoking epidemic may also explain the differences in the patterning of health behaviors according to age groups, as we observed higher contributions of smoking to the socioeconomic gradient in health in younger and middle-aged individuals compared to older individuals. A possible explanation may be that the behavioral characteristics of a given stage of the smoking epidemic have been imprinted within individuals during specific periods, resulting in a different social patterning of health behaviors across generations (Stringhini et al., 2011a; Lopez et al., 1994; Raho et al., 2015). Hence, in older generations smoking patterns may be the ones observed

Table 2
Median, minimum and maximum contribution of multiple health behaviors for associations between SEP and health outcomes. Contributions are displayed according to education, occupation, other SEP indicators (predictors - columns), and according to six major groups of study settings.

	Education	Occupation	Other SEP indicators
[a]**Outcome**			
All-cause mortality	24%[b] (−16%;43%)[c]; n = 11[d]	26% (0%;75%); n = 10	20% (−3%;55%); n = 12
Cardiovascular disorders	18% (−59%;56%); n = 21	26% (−7%;73%); n = 11	30% (−16%;69%); n = 15
Metabolic disorders	15% (−43%;67%); n = 24	29% (−6%;68%); n = 7	19% (−11%;61%); n = 23
[a]**Sex**			
Men	9% (−12%;61%); n = 13	43% (30%;69%); n = 7	26% (−3%;69%); n = 9
Women	18% (−43%;64%); n = 18	30% (9%;53%); n = 5	27% (−6%;68%); n = 14
[a]**Region**			
Central/Southern Europe	18% (−12%;42%); n = 4	10% (0%;19%); n = 2	64% (64%;64%); n = 1
Northern Europe	24% (−12%;93%); n = 23	36% (−7%;75%); n = 21	29% (−6%;69%); n = 24
North America	14% (−59%;64%); n = 24		14% (−16%;60%); n = 15
Other	26% (11%;47%); n = 12	22% (−6%;73%); n = 5	16% (−11%;47%); n = 10
[a]**Age-range**			
Young (≤35 years)	32% (32%;32%); n = 1	24% (24%;24%); n = 1	35% (23%;47%); n = 2
Middle-aged (30–65 years)	25% (−16%;50%); n = 20	36% (9%;75%); n = 18	32% (4%;69%); n = 10
Old (≥65 years)	27% (11%;67%); n = 5	36% (−7%;69%); n = 3	36% (13%;61%); n = 9
All age groups	15% (−43%;64%); n = 28	25% (−6%;73%); n = 6	16% (−16%;64%); n = 29
[a]**Type of study**			
Cross-sectional	11% (−59%;64%); n = 26	17% (−7%;53%); n = 4	14% (−16%;64%); n = 19
Longitudinal	23% (−16%;67%); n = 30	31% (0%;75%); n = 24	27% (−6%;69%); n = 31
[a]**Assessment method of health behaviors**			
Questionnaire	18% (−43%;67%); n = 54	27% (−7%;75%); n = 28	21% (−16%;64%); n = 48
Objective assessment			

[a] Study settings according to which the contribution of health behaviors was computed.
[b] Median contribution.
[c] Minimum and maximum computed contributions for each association. Contribution percentages for each association were computed according to the absolute scale difference method (Stringhini et al., 2010).
[d] Number of found associations (one study may contain several associations).

during the earlier stages of the smoking epidemic, with a relatively high prevalence of smoking and a weak socioeconomic gradient, while younger generations may be characterized by a smaller smoking prevalence and a strong social patterning of smoking (Lopez et al., 1994; Raho et al., 2015). Alternatively, age related differences in the contribution of health behaviors may also be explained by a decrease in these inequalities with ageing, as older people are more likely to have stopped smoking or decreased alcohol intake (Stringhini et al., 2012c; House et al., 1990). Nevertheless, as a consequence of the ongoing globalization process, the socioeconomic gradient in health behaviors is likely to become increasingly homogenous and omnipresent on a worldwide scale in the next years or decades. Even though we found a stronger contribution of health behaviors to social inequalities in health in Northern Europe or North America compared to other countries, increasing social differences in health behaviors are being reported in a growing number of regions, including emerging economies, as low SEP individuals are being increasingly exposed to unhealthy behaviors, including sedentary behavior and the adherence to the so-called "neoliberal diet", characterized by cheap, highly-processed and energy dense food (Schrecker, 2016; Otero et al., 2015; Prentice, 2006).

In addition to the epidemiologic transition hypothesis, the differential social patterning of health behaviors may also be related to cultural aspects and norms (Thun et al., 2012). Previous studies have suggested that the observed SEP-health behavior gradient in Northern countries may result from the expression of social distinction, while in Southern European regions, dietary patterns, alcohol intake or smoking still tend to be related to cultural norms rather than SEP (Bartley, 2004; Stringhini et al., 2011b). Moreover, in countries such as Italy, Spain or Greece, dietary patterns characterized by a high consumption of fruits, vegetables, olive oil and moderate wine intake were very common in every socioeconomic group as a result of the overall availability of these products (Bartley, 2004). Additional cultural aspects that could explain the differential social patterning of health behaviors by gender may be related to the perception of body size, standards of beauty or signs of dominance and rank (Prentice, 2006; McLaren, 2007). Previous studies have found that in low and middle income countries, men with high SEP tend to be frequently obese and adhere to health behaviors that would reflect their affluent position and lifestyle, including smoking, an energy-dense diet and sedentary behavior resulting from the use of motorized transport or leisure activities such as television watching. Alternatively, women with high SEP would tend to adopt Western standards of beauty or attractiveness, centered towards thinness and thus pay attention to their lifestyle (Stringhini et al., 2013b; Prentice, 2006; McLaren, 2007).

The stronger contribution of smoking when compared to the contribution of other health behaviors is also related to the degree of social patterning of health behaviors (Jarvis and Wardle, 2005; Lopez et al., 1994). Smoking may be so prevalent among disadvantaged SEP groups as it may help managing stress, regulating mood and dealing with every day hassles occurring as a consequence of poverty and other adverse social circumstances (Graham, 1987). Moreover, while smoking may have become stigmatized in socially advantaged individuals, in lower SEP groups smoking generally remains more tolerated (Jarvis and Wardle, 2005). Smoking uptake occurs earlier in poor children whose parents, family and peers usually smoke or may consider smoking as being the norm or socially acceptable (Jarvis and Wardle, 2005; Stuber et al., 2008).

We have also observed that the contribution of health behaviors tended to be higher when occupation was used as an exposure when compared to education and the other SEP indicators. This may be related to the fact that occupation is strongly associated to work-related stress, job strain and feelings of control (Galobardes et al., 2006; Andresen and Bouldin, 2010). Former studies have shown that these job-related psychosocial factors, particularly stress, may lead to an increased adherence to high-rewarding unhealthy behaviors, such as smoking, alcohol drinking, overeating, or drug use, which eventually

Table 3
Median, minimum and maximum contribution of smoking (Panel A) and alcohol (Panel B) for associations between SEP and health outcomes. Contributions are displayed according to education, occupation, other SEP indicators (predictors - columns), and according to six major groups of study settings.

A. Contribution by smoking	Education	Occupation	Other SEP indicators
[a]**Outcome**			
All-cause mortality	19% [b] (10%;24%) [c]; n = 7 [d]	19% (−5%;32%); n = 9	32% (13%;50%); n = 2
Cardiovascular disorders	17% (−15%;48%); n = 17	15% (−13%;36%); n = 7	14% (−11%;136%); n = 14
Metabolic disorders	14% (14%;14%); n = 1	22% (5%;35%); n = 4	15% (10%;24%); n = 3
[a]**Sex**			
Men	22% (7%;48%); n = 9	23% (14%;36%); n = 8	12% (−11%;27%); n = 5
Women	14% (−15%;23%); n = 12	6% (−13%;35%); n = 4	19% (4%;31%); n = 5
[a]**Region**			
Central/Southern Europe		4% (4%;4%); n = 1	
Northern Europe	19% (−15%;48%); n = 19	19% (−13%;36%); n = 17	17% (−11%;50%); n = 14
North America	2% (2%;2%); n = 1		35% (7%;136%); n = 4
Other	15% (10%;20%); n = 5	11% (6%;16%); n = 2	
[a]**Age-range**			
Young (≤35 years)	−7% (−15%;2%); n = 2	33% (33%;33%); n = 1	93% (50%;136%); n = 2
Middle-aged (30–65 years)	20% (4%;27%); n = 11	18% (−13%;36%); n = 17	18% (11%;31%); n = 6
Old (≥65 years)			13% (13%;13%); n = 1
All age groups	15% (4%;48%); n = 12	11% (6%;16%); n = 2	9% (−11%;24%); n = 8
[a]**Type of study**			
Cross-sectional	0% (−15%;14%); n = 3	25% (14%;35%); n = 2	7% (−11%;24%); n = 6
Longitudinal	19% (4%;48%); n = 22	17% (−13%;36%); n = 18	21% (11%;136%); n = 11
[a]**Assessment method of smoking**			
Questionnaire	17% (−15%;48%); n = 25	18% (−13%;36%); n = 20	18% (−11%;136%); n = 17
Objective assessment			29% (27%;31%); n = 2

B. Contribution by alcohol	Education	Occupation	Other SEP indicators
Outcome			
All-cause mortality	−2% (−11%;10%); n = 3	12% (7%;13%); n = 4	17% (17%;17%); n = 1
Cardiovascular disorders	6% (−2%;21%); n = 8	10% (3%;18%); n = 2	56% (−2%;261%); n = 6
Metabolic disorders		2% (2%;2%); n = 2	
Sex			
Men	−4% (−6%;−2%); n = 2		21% (−2%;43%); n = 2
Women	5% (−11%;21%); n = 5		11% (6%;24%); n = 3
Region			
Central/Southern Europe		7% (7%;7%); n = 1	
Northern Europe	5% (−11%;21%); n = 9	9% (2%;18%); n = 5	15% (−2%;43%); n = 4
North America	2% (2%;2%); n = 1		139% (17%;261%); n = 2
Other	5% (5%;5%); n = 1	7% (3%;12%); n = 2	
Age-range			
Young (≤35 years)	3% (3%;3%); n = 1	2% (2%;2%); n = 1	261% (261%;261%); n = 1
Middle-aged (30–65 years)	0% (−11%;21%); n = 6	10% (2%;18%); n = 7	16% (−2%;43%); n = 3
Old (≥65 years)			17% (17%;17%); n = 1
All age groups	12% (5%;19%); n = 4		18% (11%;24%); n = 2
Type of study			
Cross-sectional	3% (2%;3%); n = 2		
Longitudinal	6% (−11%;21%); n = 9	9% (2%;18%); n = 8	50% (−2%;261%); n = 7
Assessment method of alcohol			
Questionnaire	4% (−11%;21%); n = 11	9% (2%;18%); n = 8	71% (11%;261%); n = 5
Objective assessment			

[a] Study settings according to which the contribution of smoking/alcohol was computed.
[b] Median contribution.
[c] Minimum and maximum computed contributions for each association. Contribution percentages for each association were computed according to the absolute scale difference method (Stringhini et al., 2010).
[d] Number of found associations (one study may contain several associations).

lead to adverse health outcomes (Wardle and Steptoe, 2003; Wilkinson and Marmot, 2003).

4.2. Physiological aspects

The contribution of health behaviors to the socioeconomic gradient in health also varied depending on the health outcome. This may be related to the fact that some physiological systems are more affected by certain types of behaviors than others. For example, smoking would have greater consequences on occurrence of respiratory diseases, malignancies and atherosclerosis than on obesity, which tends to be more related to dietary patterns and physical activity (Shamshirgaran et al., 2013; Dinwiddie et al., 2014). Furthermore, the contribution of genetic factors varies from one health outcome to another, thus moderating or interfering with the impact of health behaviors (Pilia et al., 2006; Elbein et al., 1999; Mayer et al., 2007; Maskarinec and Noh, 2004).

Table 4
Median, minimum and maximum contribution of physical activity (Panel A) and dietary patterns (Panel B) for associations between SEP and health outcomes. Contributions are displayed according to education, occupation, other SEP indicators (predictors - columns), and according to six major groups of study settings.

A. Contribution by physical activity	Education	Occupation	Other SEP indicators
[a]**Outcome**			
All-cause mortality	12%[b] (8%;17%)[c]; n = 3[d]	20% (8%;21%); n = 3	17% (17%;17%); n = 1
Cardiovascular disorders	4% (−5%;13%); n = 12	12% (12%;12%); n = 1	8% (−33%;34%); n = 5
Metabolic disorders	9% (9%;9%); n = 1	6% (4%;10%); n = 4	
[a]**Sex**			
Men	4% (0%;13%); n = 4	10% (10%;10%); n = 1	15% (3%;27%); n = 2
Women	6% (0%;11%); n = 7	4% (4%;4%); n = 1	9% (9%;9%); n = 1
[a]**Region**			
Central/Southern Europe		8% (8%;8%); n = 1	
Northern Europe	6% (0%;17%); n = 13	11% (4%;21%); n = 7	13% (3%;27%); n = 3
North America	-2% (−5%;1%); n = 2		6% (−33%;34%); n = 3
Other	9% (9%;9%); n = 1		
[a]**Age-range**			
Young (≤35 years)	1% (1%;1%); n = 1	4% (4%;4%); n = 1	34% (34%;34%); n = 1
Middle-aged (30–65 years)	7% (−5%;13%); n = 7	13% (4%;21%); n = 7	15% (3%;27%); n = 2
Old (≥65 years)			17% (17%;17%); n = 1
All age groups	5% (0%;17%); n = 8		−12% (−33%;9%); n = 2
[a]**Type of study**			
Cross-sectional	2% (−5%;9%); n = 3	7% (4%;10%); n = 2	
Longitudinal	6% (0%;17%); n = 13	14% (4%;21%); n = 6	18% (3%;34%); n = 5
[a]**Assessment method of health behaviors**			
Questionnaire	6% (−5%;17%); n = 16	12% (4%;21%); n = 8	18% (3%;34%); n = 5
Objective assessment			

B. Contribution by diet	Education	Occupation	Other SEP indicators
Outcome			
All-cause mortality	21%[a] (17%;25%)[b]; n = 2[c]	17% (4%;24%); n = 3	
Cardiovascular disorders	24% (2%;50%); n = 5	7% (7%;7%); n = 1	
Metabolic disorders		10% (8%;11%); n = 2	11% (11%;11%); n = 1
Sex			
Men	36% (25%;50%); n = 3		
Women	11% (6%;17%); n = 2		
Region			
Central/Southern Europe		4% (4%;4%); n = 1	
Northern Europe	26% (6%;50%); n = 5	13% (7%;24%); n = 5	
North America	29% (29%;29%); n = 1		11% (11%;11%); n = 1
Other	2% (2%;2%); n = 1		
Age-range			
Young (≤35 years)		11% (11%;11%); n = 1	
Middle-aged (30–65 years)	27% (6%;50%); n = 6	13% (4%;24%); n = 5	
Old (≥65 years)			
All age groups	2% (2%;2%); n = 1		11% (11%;11%); n = 1
Type of study			
Cross-sectional	29% (29%;29%); n = 1		11% (11%;11%); n = 1
Longitudinal	22% (2%;50%); n = 6	13% (4%;24%); n = 6	
Assessment method of diet			
Questionnaire	23% (2%;50%); n = 7	13% (4%;24%); n = 6	11% (11%;11%); n = 1
Objective assessment			

[a] Study settings according to which the contribution of physical activity/diet was computed.
[b] Median contribution.
[c] Minimum and maximum computed contributions for each association. Contribution percentages for each association were computed according to the absolute scale difference method ().
[d] Number of found associations (one study may contain several associations).

4.3. Methodological aspects

Methodological aspects can also explain heterogeneity across studies. Health behaviors may explain a larger proportion of the SEP-health gradient when their assessment is repeated and thus more accurate over time, as in longitudinal studies (Stringhini et al., 2010). The contribution of health behaviors may also vary depending on the specific confounders or modifying factors that are controlled for in the various studies (Stringhini et al., 2011b).

Finally, we have seen that health behaviors contribute to varying degrees to SEP differences in health, the main reason being the differential social patterning of health behaviors which is due to cultural, political or demographic factors. However, it is important to note that health behaviors do not entirely explain the socioeconomic gradient in health. Other mediators including psychosocial factors, working conditions, environmental exposures as well as access to healthcare likely

constitute additional mechanisms through which SEP affects health, and the study of their contribution, along with health behaviors, may help understand the SEP gradient globally.

4.4. Strengths and limitations

To our knowledge, this is the first study to have systematically reviewed the evidence on the contribution of health behaviors to socioeconomic inequalities in health. Our study has limitations to acknowledge. All the studies included in this review assume a causal association between socioeconomic factors and health. Although the majority of studies were longitudinal studies conducted on healthy individuals where the exposure preceded the outcome, reverse causation cannot be completely ruled out, especially for cross-sectional studies which are less well suited for determining causal associations (Wilkinson and Marmot, 2003; Hellgren and Sverke, 2003; Zapf et al., 1996). While the causal association from health towards SEP was generally found to be negligible when compared to the causal association going from SEP towards health (Wilkinson and Marmot, 2003; Blane et al., 1993; Marmot, 2015), some former studies have reported that children showing evidence of illness were more likely to be downwardly mobile in the socioeconomic structure in later life (Wilkinson and Marmot, 2003; Wadsworth, 1986; Power et al., 1990). Another limitation is the frequent uneven distribution of studies across categories of different aggregating factors (study region, age-range, type of study, assessment method of health behaviors), which challenges interpretation and identification of factors that affect the contribution of health behaviors. Further, differences in the set of confounders included in the analysis across studies may represent an additional source of heterogeneity. Another limitation of this work concerns the use of the absolute difference method to compute the contribution of health behaviors, as this method does not take into account all the possible confounding and interactions between the exposure, the mediators and the outcomes, and is therefore subject to bias (VanderWeele, 2016). Only nine papers used alternative mediation methods, of which two applied the counterfactual mediation methods based on direct and indirect effects (Nordahl et al., 2014a; Nordahl et al., 2014b), which restrict bias by including all possible confounding between the exposure, the mediators and the outcome. Moreover, an additional limitation may be related to the fact that some of the included studies used BMI as a risk factor or a proxy for diet, while other studies used it as an outcome. This differential use of BMI may further challenge the interpretation of the contribution of health behaviors, as BMI was not used consistently across the included studies. Furthermore, differences in sociodemographic aspects, study-periods, and assessment methods of SEP indicators, health behaviors, and health outcomes, greatly challenge between-study comparisons of the contribution of health behaviors to the SEP gradient in health, and preclude conducting formal meta-analyses and assessing associated parameters (i.e. publication bias, quality score). Consequently, this heterogeneity may hinder an adequate interpretation of the contribution of health behaviors and prevent drawing right conclusions (Higgins and Thompson, 2002; Higgins et al., 2003). The use of objective and validated measurement and classification methods such as the European socio-economic classification scheme (ESEC) for classifying socioeconomic position, accelerometer or cotinine levels for assessing health behaviors, and clinical parameters and medical records for determining health outcomes, should be preferred over less valid and inaccurate methods (i.e. self-report), in order to limit bias and further improve the quality of studies (Bartley, 2004; Benowitz, 1996; Petrovic et al., 2016; Prince et al., 2008; Rose and Harrison, 2007). However, we did not assess additional aspects related to study quality in this systematic review, such as comprehensive reporting of results, or the validity and reliability of questionnaire, which may potentially represent a limitation in terms of study comparison. Additionally, longitudinal designs should be preferred over the cross-sectional ones, as they allow to determine causality and mediation, and account for the fact that the assessment of health outcomes, the adherence to health behaviors, and the socioeconomic position evolve over the life-course and follow secular trends, as suggested by the epidemiologic transition and the smoking epidemic model (Stringhini et al., 2010; Galobardes et al., 2006; Lopez et al., 1994; Forouhi et al., 2006; Association AD, 2014; Messerli et al., 2007). Finally, another potential issue may be related to the contribution of multiple health behaviors when compared to the contribution of individual health behaviors, as we cannot exclude potential non-additive effects (i.e. interaction between health behaviors) in models adjusting for multiple health behaviors, which may affect or bias the extent of the contribution of health behaviors.

5. Conclusion

This is the first study to provide a complete and comprehensive synthesis on the factors influencing the contribution of health behaviors to the socioeconomic gradient in health. We observed that health behaviors overall contribute to the association between SEP and health outcomes, but that this contribution varies substantially according to geographic location, sex, age, health outcomes and methodological differences between included studies, the main reason for this heterogeneity being the differential socioeconomic patterning of health behaviors in given regional and demographic contexts. While our results provide a global understanding of the role of health behaviors to the socioeconomic gradient in health, they also encourage implementation of policies aimed at reducing socioeconomic inequalities in health, for example addressing the unequal distribution of unhealthy behaviors.

An overall challenge regarding the socioeconomic gradient in health would be to identify all the mediators involved in this association, such as psychosocial factors, material conditions, environmental exposures or work conditions in order to provide a global and complete understanding of mechanisms underlying socioeconomic inequalities in health. Finally, an experimental approach and monitoring regarding the effectiveness of these policies should also be considered to ensure that socioeconomic inequalities are indeed reduced.

Compliance with ethical standards

For this type of study ethics approval is not required.

Conflicts of interest

None.

Acknowledgments

The authors would like to express their gratitude to Professor Katherine Frohlich (University of Montreal) and Professor Mauricio Avendano Pabon (University of Harvard) for helping improve this manuscript. The authors would also like to thank all the collaborators of the Lifepath project (http://www.lifepathproject.eu/).

Funding

This work is supported by the Lifepath project, which is funded by the European commission and the Swiss State Secretariat for Education, Research and Innovation - SERI (Horizon 2020 grant n° 633666). Silvia Stringhini is supported by the Swiss National Science Foundation (Ambizione Grant n° PZ00P3_167732). The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; and preparation, review or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2018.05.003.

References

Adler, N.E., Boyce, W.T., Chesney, M.A., Folkman, S., Syme, S.L., 1993. Socioeconomic inequalities in health. No easy solution. JAMA 269 (24), 3140–3145.

Agardh, E.E., Ahlbom, A., Andersson, T., Efendic, S., Grill, V., Hallqvist, J., et al., 2004. Explanations of socioeconomic differences in excess risk of type 2 diabetes in Swedish men and women. Diabetes Care 27 (3), 716–721.

Agardh, E., Ahlbom, A., Andersson, T., Efendic, S., Grill, V., Hallqvist, J., et al., 2007. Socio-economic position at three points in life in association with type 2 diabetes and impaired glucose tolerance in middle-aged Swedish men and women. Int. J. Epidemiol. 36 (1), 84–92.

Andresen, E., Bouldin, E.D., 2010. Public Health Foundations: Concepts and Practices. John Wiley & Sons.

Antonovsky, A., 1967. Social class, life expectancy and overall mortality. Milbank Mem. Fund Q. 45 (2), 31–73.

Aslanyan, S., Weir, C.J., Lees, K.R., Reid, J.L., McInnes, G.T., 2003. Effect of area-based deprivation on the severity, subtype, and outcome of ischemic stroke. Stroke 34 (11), 2623–2628.

Association AD, 2014. Diagnosis and classification of diabetes mellitus. Diabetes Care 37 (Supplement 1), S81–S90.

Avendano, M., Kunst, A.E., Huisman, M., Lenthe, F.V., Bopp, M., Regidor, E., et al., 2006a. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. Heart 92 (4), 461–467.

Avendano, M., Kawachi, I., Van Lenthe, F., Boshuizen, H.C., Mackenbach, J.P., Van den Bos, G., et al., 2006b. Socioeconomic status and stroke incidence in the US elderly the role of risk factors in the EPESE study. Stroke 37 (6), 1368–1373.

Bank W, 2016. Countries and Economies: World Bank. Available from. http://data.worldbank.org/country.

Bartley, M., 2004. Health Inequality: An Introduction to Theories, Concepts and Methods.

Bartley, M., 2016. Health Inequality: An Introduction to Concepts, Theories and Methods. John Wiley & Sons.

Beauchamp, A., Peeters, A., Wolfe, R., Turrell, G., Harriss, L.R., Giles, G.G., et al., 2010. Inequalities in cardiovascular disease mortality: the role of behavioural, physiological and social risk factors. J. Epidemiol. Community Health 64 (6), 542–548.

Benowitz, N.L., 1996. Cotinine as a biomarker of environmental tobacco smoke exposure. Epidemiol. Rev. 18 (2), 188–204.

Bihan, H., Backholer, K., Peeters, A., Stevenson, C.E., Shaw, J.E., Magliano, D.J., 2016. Socioeconomic position and premature mortality in the AusDiab cohort of Australian adults. Am. J. Public Health 106 (3), 470–477.

Blakely, T., Wilson, N., 2005. The contribution of smoking to inequalities in mortality by education varies over time and by sex: two national cohort studies, 1981–84 and 1996–99. Int. J. Epidemiol. 34 (5), 1054–1062.

Blane, D., Smith, G.D., Bartley, M., 1993. Social selection: what does it contribute to social class differences in health? Sociol. Health Illn. 15 (1), 1–15.

Bonaccio, M., Di Castelnuovo, A., Costanzo, S., Persichillo, M., Donati, M.B., De Gaetano, G., et al., 2016. Interaction between education and income on the risk of all-cause mortality: prospective results from the MOLI-SANI study. Int. J. Public Health 1–12.

Bradley Deere, M., Seth, Lirette M., 2016. Life course socioeconomic position and subclinical disease: the Jackson heart study. Ethn. Dis. 26 (3), 355.

Brancati, F.L., Whelton, P.K., Kuller, L.H., Klag, M.J., 1996. Diabetes mellitus, race, and socioeconomic status a population-based study. Ann. Epidemiol. 6 (1), 67–73.

Brummett, B.H., Babyak, M.A., Siegler, I.C., Shanahan, M., Harris, K.M., Elder, G.H., et al., 2011. Systolic blood pressure, socioeconomic status, and biobehavioral risk factors in a nationally representative US young adult sample. Hypertension 58 (2), 161–166.

Centers for Disease C, Prevention, 2008. Smoking-attributable mortality, years of potential life lost, and productivity losses–United States, 2000–2004. MMWR Morb. Mortal. Wkly Rep. 57 (45), 1226–1228.

Chaix, B., Bean, K., Leal, C., Thomas, F., Havard, S., Evans, D., et al., 2010. Individual/neighborhood social factors and blood pressure in the RECORD cohort study which risk factors explain the associations? Hypertension 55 (3), 769–775.

Chandola, T., 1998. Social inequality in coronary heart disease: a comparison of occupational classifications. Soc. Sci. Med. 47 (4), 525–533.

Chapman, B.P., Fiscella, K., Kawachi, I., Duberstein, P.R., 2010. Personality, socioeconomic status, and all-cause mortality in the United States. Am. J. Epidemiol. 171 (1), 83–92.

Chinn, D.J., White, M., Harland, J., Drinkwater, C., Raybould, S., 1999. Barriers to physical activity and socioeconomic position: implications for health promotion. J. Epidemiol. Community Health 53 (3), 191.

Curtin, F., Morabia, A., Bernstein, M., 1997. Smoking behavior in a Swiss urban population: the role of gender and education. Prev. Med. 26 (5), 658–663.

Demakakos, P., Marmot, M., Steptoe, A., 2012. Socioeconomic position and the incidence of type 2 diabetes: the ELSA study. Eur. J. Epidemiol. 27 (5), 367–378.

Dinca-Panaitescu, S., Dinca-Panaitescu, M., Bryant, T., Daiski, I., Pilkington, B., Raphael, D., 2011. Diabetes prevalence and income: results of the Canadian community health survey. Health Policy 99 (2), 116–123.

Dinca-Panaitescu, M., Dinca-Panaitescu, S., Raphael, D., Bryant, T., Pilkington, B., Daiski, I., 2012. The dynamics of the relationship between diabetes incidence and low income: longitudinal results from Canada's National Population Health Survey. Maturitas 72 (3), 229–235.

Dinwiddie, G.Y., Zambrana, R.E., Garza, M.A., 2014. Exploring risk factors in Latino cardiovascular disease: the role of education, nativity, and gender. Am. J. Public Health 104 (9), 1742–1750.

Doll, R., Hill, A.B., 1950. Smoking and carcinoma of the lung. Br. Med. J. 2 (4682), 739.

Dupre, M.E., Silberberg, M., Willis, J.M., Feinglos, M.N., 2015. Education, glucose control, and mortality risks among US older adults with diabetes. Diabetes Res. Clin. Pract. 107 (3), 392–399.

Egeland, G.M., Tverdal, A., Meyer, H.E., Selmer, R., 2002. A man's heart and a wife's education: a 12-year coronary heart disease mortality follow-up in Norwegian men. Int. J. Epidemiol. 31 (4), 799–805.

Elbein, S.C., Hasstedt, S.J., Wegner, K., Kahn, S.E., 1999. Heritability of pancreatic β-cell function among nondiabetic members of Caucasian familial type 2 diabetic Kindreds 1. J. Clin. Endocrinol. Metab. 84 (4), 1398–1403.

Feinglass, J., Lin, S., Thompson, J., Sudano, J., Dunlop, D., Song, J., et al., 2007. Baseline health, socioeconomic status, and 10-year mortality among older middle-aged Americans: findings from the health and retirement study, 1992–2002. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 62 (4) S209-S17.

Floud, S., Balkwill, A., Moser, K., Reeves, G.K., Green, J., Beral, V., et al., 2016. The role of health-related behavioural factors in accounting for inequalities in coronary heart disease risk by education and area deprivation: prospective study of 1.2 million UK women. BMC Med. 14 (1), 145.

Forouhi, N., Balkau, B., Borch-Johnsen, K., Dekker, J., Glumer, C., Qiao, Q., et al., 2006. The threshold for diagnosing impaired fasting glucose: a position statement by the European Diabetes Epidemiology Group. Diabetologia 49 (5), 822–827.

Franks, P., Winters, P.C., Tancredi, D.J., Fiscella, K.A., 2011. Do changes in traditional coronary heart disease risk factors over time explain the association between socioeconomic status and coronary heart disease? BMC Cardiovasc. Disord. 11 (1), 1.

Fu, C., Chen, Y., Wang, F., Wang, X., Song, J., Jiang, Q., 2011. High prevalence of hyperglycaemia and the impact of high household income in transforming Rural China. BMC Public Health 11 (1), 1.

Galobardes, B., Shaw, M., Lawlor, D.A., Lynch, J.W., Smith, G.D., 2006. Indicators of socioeconomic position (part 1). J. Epidemiol. Community Health 60 (1), 7–12.

Giesinger, I., Goldblatt, P., Howden-Chapman, P., Marmot, M., Kuh, D., Brunner, E., 2013. Association of socioeconomic position with smoking and mortality: the contribution of early life circumstances in the 1946 birth cohort. J. Epidemiol. Community Health 68 (3), 275–279 jech-2013-203159.

Gliksman, M.D., Kawachi, I., Hunter, D., Colditz, G.A., Manson, J., Stampfer, M.J., et al., 1995. Childhood socioeconomic status and risk of cardiovascular disease in middle aged US women: a prospective study. J. Epidemiol. Community Health 49 (1), 10–15.

Gorman, B.K., Sivaganesan, A., 2007. The role of social support and integration for understanding socioeconomic disparities in self-rated health and hypertension. Soc. Sci. Med. 65 (5), 958–975.

Graham, H., 1987. Women's smoking and family health. Soc. Sci. Med. 25 (1), 47–56.

Gustafsson, P.E., Persson, M., Hammarström, A., 2011. Life course origins of the metabolic syndrome in middle-aged women and men: the role of socioeconomic status and metabolic risk factors in adolescence and early adulthood. Ann. Epidemiol. 21 (2), 103–110.

Hagger-Johnson, G., Roberts, B., Boniface, D., Sabia, S., Batty, G.D., Elbaz, A., et al., 2012. Neuroticism and cardiovascular disease mortality: socioeconomic status modifies the risk in women (UK Health and Lifestyle Survey). Psychosom. Med. 74 (6), 596–603.

Hart, C.L., Hole, D.J., Smith, G.D., 2000. The contribution of risk factors to stroke differentials, by socioeconomic position in adulthood: the Renfrew/Paisley Study. Am. J. Public Health 90 (11), 1788.

Hellgren, J., Sverke, M., 2003. Does job insecurity lead to impaired well-being or vice versa? Estimation of cross-lagged effects using latent variable modelling. J. Organ. Behav. 24 (2), 215–236.

Helmert, U., Shea, S., 1994. Social inequalities and health status in Western Germany. Public Health 108 (5), 341–356.

Higgins, J., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ [Br. Med. J.] 327 (7414), 557.

Hitchman, S.C., Fong, G.T., 2011. Gender empowerment and female-to-male smoking prevalence ratios. Bull. World Health Organ. 89 (3), 195–202.

Houle, J., Lauzier-Jobin, F., Beaulieu, M.-D., Meunier, S., Coulombe, S., Côté, J., et al., 2016. Socioeconomic status and glycemic control in adult patients with type 2 diabetes: a mediation analysis. BMJ Open Diabetes Res. Care 4 (1), e000184.

House, J.S., Kessler, R.C., Herzog, A.R., 1990. Age, socioeconomic status, and health. Milbank Q. 383–411.

Huisman, M., Kunst, A., Mackenbach, J., 2005. Educational inequalities in smoking among men and women aged 16 years and older in 11 European countries. Tob. Control. 14 (2), 106–113.

Hwang, J., Shon, C., 2014. Relationship between socioeconomic status and type 2 diabetes: results from Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2012. BMJ Open 4 (8), e005710.

Ito, S., Takachi, R., Inoue, M., Kurahashi, N., Iwasaki, M., Sasazuki, S., et al., 2008. Education in relation to incidence of and mortality from cancer and cardiovascular disease in Japan. Eur. J. Pub. Health 18 (5), 466–472.

Jacobsen, B.K., Thelle, D.S., 1988. Risk factors for coronary heart disease and level of education the Tromsø heart study. Am. J. Epidemiol. 127 (5), 923–932.

Jarvis, M.J., Wardle, J., 2005. Social Patterning of Individual Health Behaviours: The Case of Cigarette Smoking.

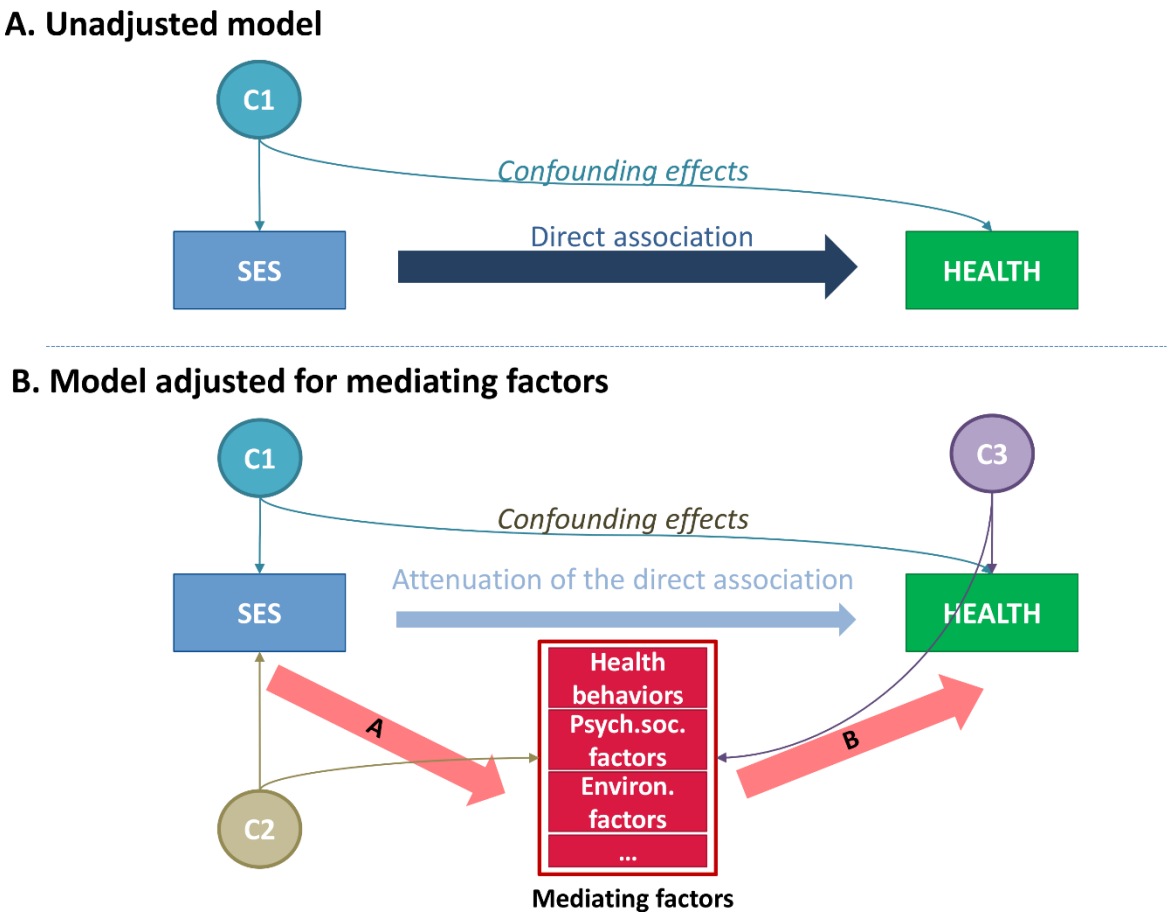
Jeffery, R.W., French, S.A., Forster, J.L., Spry, V.M., 1991. Socioeconomic status differences in health behaviors related to obesity: the healthy worker project. Int. J. Obes. 15 (10), 689–696.

Kavanagh, A., Bentley, R.J., Turrell, G., Shaw, J., Dunstan, D., Subramanian, S., 2010. Socioeconomic position, gender, health behaviours and biomarkers of cardiovascular disease and diabetes. Soc. Sci. Med. 71 (6), 1150–1160.
Khang, Y.-H., Kim, H.R., 2005. Explaining socioeconomic inequality in mortality among South Koreans: an examination of multiple pathways in a nationally representative longitudinal study. Int. J. Epidemiol. 34 (3), 630–637.
Khang, Y.-H., Lynch, J.W., Yang, S., Harper, S., Yun, S.-C., Jung-Choi, K., et al., 2009. The contribution of material, psychosocial, and behavioral factors in explaining educational and occupational mortality inequalities in a nationally representative sample of South Koreans: relative and absolute perspectives. Soc. Sci. Med. 68 (5), 858–866.
Kilander, L., Berglund, L., Boberg, M., Vessby, B., Lithell, H., 2001. Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men. Int. J. Epidemiol. 30 (5), 1119–1126.
Kittleson, M.M., Meoni, L.A., Wang, N.-Y., Chu, A.Y., Ford, D.E., Klag, M.J., 2006. Association of childhood socioeconomic status with subsequent coronary heart disease in physicians. Arch. Intern. Med. 166 (21), 2356–2361.
Kivimäki, M., Lawlor, D.A., Smith, G.D., Kouvonen, A., Virtanen, M., Elovainio, M., et al., 2007. Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish public sector study. Am. J. Public Health 97 (5), 874–879.
Klatsky, A.L., Armstrong, M.A., Friedman, G.D., 1992. Alcohol and mortality. Ann. Intern. Med. 117 (8), 646–654.
Krieger, N., Williams, D.R., Moss, N.E., 1997. Measuring social class in US public health research: concepts, methodologies, and guidelines. Annu. Rev. Public Health 18 (1), 341–378.
Krishnan, S., Cozier, Y.C., Rosenberg, L., Palmer, J.R., 2010. Socioeconomic status and incidence of type 2 diabetes: results from the Black Women's Health Study. Am. J. Epidemiol. 171 (5), 564–570 kwp443.
Kuh, D., Ben-Shlomo, Y., Lynch, J., Hallqvist, J., Power, C., 2003. Life course epidemiology. J. Epidemiol. Community Health 57 (10), 778.
Kuh, D., Karunananthan, S., Bergman, H., Cooper, R., 2014. A life-course approach to healthy ageing: maintaining physical capability. Proc. Nutr. Soc. 73 (02), 237–248.
Kuper, H., Adami, H.-O., Theorell, T., Weiderpass, E., 2007. The socioeconomic gradient in the incidence of stroke a prospective study in middle-aged women in Sweden. Stroke 38 (1), 27–33.
Laaksonen, M., Prättälä, R., Helasoja, V., Uutela, A., Lahelma, E., 2003. Income and health behaviours. Evidence from monitoring surveys among Finnish adults. J. Epidemiol. Community Health 57 (9), 711–717.
Laaksonen, M., Talala, K., Martelin, T., Rahkonen, O., Roos, E., Helakorpi, S., et al., 2008. Health behaviours as explanations for educational level differences in cardiovascular and all-cause mortality: a follow-up of 60,000 men and women over 23 years. Eur. J. Pub. Health 18 (1), 38–43.
Lantz, P.M., House, J.S., Lepkowski, J.M., Williams, D.R., Mero, R.P., Chen, J., 1998. Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults. JAMA 279 (21), 1703–1708.
Lantz, P.M., Golberstein, E., House, J.S., Morenoff, J., 2010. Socioeconomic and behavioral risk factors for mortality in a national 19-year prospective study of US adults. Soc. Sci. Med. 70 (10), 1558–1566.
László, K.D., Janszky, I., Ahnve, S., 2008. Income and recurrent events after a coronary event in women. Eur. J. Epidemiol. 23 (10), 669–680.
Lawlor, D.A., Smith, G.D., Ebrahim, S., 2004. Association between childhood socioeconomic status and coronary heart disease risk among postmenopausal women: findings from the British Women's heart and health study. Am. J. Public Health 94 (8), 1386–1392.
Lear, S.A., Teo, K., Gasevic, D., Zhang, X., Poirier, P.P., Rangarajan, S., et al., 2014. The association between ownership of common household devices and obesity and diabetes in high, middle and low income countries. Can. Med. Assoc. J. 186 (4), 258–266.
Lipowicz, A., Szklarska, A., Malina, R.M., 2014. Allostatic load and socioeconomic status in Polish adult men. J. Biosoc. Sci. 46 (02), 155–167.
Lopez, A.D., Collishaw, N.E., Piha, T., 1994. A descriptive model of the cigarette epidemic in developed countries. Tob. Control. 3 (3), 242.
Loucks, E.B., Rehkopf, D.H., Thurston, R.C., Kawachi, I., 2007. Socioeconomic disparities in metabolic syndrome differ by gender: evidence from NHANES III. Ann. Epidemiol. 17 (1), 19–26.
Lynch, J.W., Kaplan, G.A., Cohen, R.D., Tuomilehto, J., Salonen, J.T., 1996. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? Am. J. Epidemiol. 144 (10), 934–942.
Macintyre, S., 2000. The social patterning of exercise behaviours: the role of personal and local resources. Br. J. Sports Med. 34 (1), 6.
Mackenbach, J.P., Kunst, A.E., Cavelaars, A.E., Groenhof, F., Geurts, J.J., 1997. Health EWGoSIi. Socioeconomic inequalities in morbidity and mortality in Western Europe. Lancet 349 (9066), 1655–1659.
Mackenbach, J.P., Stirbu, I., Roskam, A.-J.R., Schaap, M.M., Menvielle, G., Leinsalu, M., et al., 2008. Socioeconomic inequalities in health in 22 European countries. N. Engl. J. Med. 358 (23), 2468–2481.
Mäki, N.E., Martikainen, P.T., Eikemo, T., Menvielle, G., Lundberg, O., Östergren, O., et al., 2014. The potential for reducing differences in life expectancy between educational groups in five European countries: the effects of obesity, physical inactivity and smoking. J. Epidemiol. Community Health 68, 635–640 jech-2013-203501.
Manuck, S.B., Phillips, J., Gianaros, P.J., Flory, J.D., Muldoon, M.F., 2010. Subjective socioeconomic status and presence of the metabolic syndrome in midlife community volunteers. Psychosom. Med. 72 (1), 35.
Marmot, M., 2015. The Health Gap: The Challenge of an Unequal World. Bloomsbury Publishing.
Marmot, M.G., Adelstein, A.M., Robinson, N., Rose, G.A., 1978. Changing social-class distribution of heart disease. Br. Med. J. 2 (6145), 1109–1112.
Marmot, M., Shipley, M., Hemingway, H., Head, J., Brunner, E., 2008. Biological and behavioural explanations of social inequalities in coronary heart disease: the Whitehall II study. Diabetologia 51 (11), 1980–1988.
Maskarinec, G., Noh, J.J., 2004. The effect of migration on cancer incidence among Japanese in Hawaii. Ethn. Dis. 14 (3), 431–439.
Matthews, K.A., Gallo, L.C., Taylor, S.E., 2010. Are psychosocial factors mediators of socioeconomic status and health connections? Ann. N. Y. Acad. Sci. 1186 (1), 146–173.
Maty, S.C., Everson-Rose, S.A., Haan, M.N., Raghunathan, T.E., Kaplan, G.A., 2005. Education, income, occupation, and the 34-year incidence (1965–99) of type 2 diabetes in the Alameda County study. Int. J. Epidemiol. 34 (6), 1274–1281.
Maty, S.C., Lynch, J.W., Raghunathan, T.E., Kaplan, G.A., 2008. Childhood socioeconomic position, gender, adult body mass index, and incidence of type 2 diabetes mellitus over 34 years in the Alameda County study. Am. J. Public Health 98 (8), 1486–1494.
Maty, S.C., James, S.A., Kaplan, G.A., 2010. Life-course socioeconomic position and incidence of diabetes mellitus among blacks and whites: the Alameda County study, 1965–1999. Am. J. Public Health 100 (1), 137–145.
Mayer, B., Erdmann, J., Schunkert, H., 2007. Genetics and heritability of coronary artery disease and myocardial infarction. Clin. Res. Cardiol. 96 (1), 1–7.
McFadden, E., Luben, R., Wareham, N., Bingham, S., Khaw, K.-T., 2008. Occupational social class, educational level, smoking and body mass index, and cause-specific mortality in men and women: a prospective study in the European prospective investigation of cancer and nutrition in Norfolk (EPIC-Norfolk) cohort. Eur. J. Epidemiol. 23 (8), 511–522.
McFadden, E., Luben, R., Wareham, N., Bingham, S., Khaw, K.-T., 2009. Social class, risk factors, and stroke incidence in men and women a prospective study in the European prospective investigation into cancer in Norfolk cohort. Stroke 40 (4), 1070–1077.
McLaren, L., 2007. Socioeconomic status and obesity. Epidemiol. Rev. 29 (1), 29–48.
Messerli, F.H., Williams, B., Ritz, E., 2007. Essential hypertension. Lancet 370 (9587), 591–603.
Miranda, J.J., Kinra, S., Casas, J.P., Davey Smith, G., Ebrahim, S., 2008. Non-communicable diseases in low-and middle-income countries: context, determinants and health policy. Tropical Med. Int. Health 13 (10), 1225–1234.
Montez, J.K., Bromberger, J.T., Harlow, S.D., Kravitz, H.M., Matthews, K.A., 2016. Life-course socioeconomic status and metabolic syndrome among midlife women. J. Gerontol. B Psychol. Sci. Soc. Sci. 71, 1097–1107 gbw014.
Münster, E., Rüger, H., Ochsmann, E., Letzel, S., Toschke, A.M., 2009. Over-indebtedness as a marker of socioeconomic status and its association with obesity: a cross-sectional study. BMC Public Health 9 (1), 1.
Næss, Ø., Piro, F.N., Nafstad, P., Smith, G.D., Leyland, A.H., 2007. Air pollution, social deprivation, and mortality: a multilevel cohort study. Epidemiology 18 (6), 686–694.
Nandi, A., Glymour, M.M., Subramanian, S., 2014. Association among socioeconomic status, health behaviors, and all-cause mortality in the United States. Epidemiology 25 (2), 170–177.
Ni, L.F., Dai, Y.T., Su, T.C., Hu, W.Y., 2013. Substance use, gender, socioeconomic status and metabolic syndrome among adults in Taiwan. Public Health Nurs. 30 (1), 18–28.
Niedhammer, I., Bourgkard, E., Chau, N., Group LS, 2011. Occupational and behavioural factors in the explanation of social inequalities in premature and total mortality: a 12.5-year follow-up in the Lorhandicap study. Eur. J. Epidemiol. 26 (1), 1–12.
Nocon, M., Keil, T., Willich, S.N., 2007. Education, income, occupational status and health risk behaviour. J. Public Health 15 (5), 401–405.
Nordahl, H., Rod, N.H., Frederiksen, B.L., Andersen, I., Lange, T., Diderichsen, F., et al., 2014a. Education and risk of coronary heart disease: assessment of mediation by behavioral risk factors using the additive hazards model (vol 28, pg 149, 2013). Eur. J. Epidemiol. 29 (4), 303–306.
Nordahl, H., Lange, T., Osler, M., Diderichsen, F., Andersen, I., Prescott, E., et al., 2014b. Education and cause-specific mortality: the mediating role of differential exposure and vulnerability to behavioral risk factors. Epidemiology 25 (3), 389–396.
Notkola, V., Punsar, S., Karvonen, M., Haapakoski, J., 1985. Socio-economic conditions in childhood and mortality and morbidity caused by coronary heart disease in adulthood in rural Finland. Soc. Sci. Med. 21 (5), 517–523.
Omran, A.R., 2005. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Q. 83 (4), 731–757.
van Oort, F.V., van Lenthe, F.J., Mackenbach, J.P., 2004. Cooccurrence of lifestyle risk factors and the explanation of education inequalities in mortality: results from the GLOBE study. Prev. Med. 39 (6), 1126–1134.
van Oort, F.V., van Lenthe, F.J., Mackenbach, J.P., 2005. Material, psychosocial, and behavioural factors in the explanation of educational inequalities in mortality in The Netherlands. J. Epidemiol. Community Health 59 (3), 214–220.
Osler, M., Christensen, U., Due, P., Lund, R., Andersen, I., Diderichsen, F., et al., 2003. Income inequality and ischaemic heart disease in Danish men and women. Int. J. Epidemiol. 32 (3), 375–380.
Otero, G., Pechlaner, G., Liberman, G., Gürcan, E.C., 2015. Food security and inequality: measuring the risk of exposure to the neoliberal diet. In: Simons Papers in Security and Development. 42. pp. 2015.
Paffenbarger Jr., R.S., Hyde, R., Wing, A.L., Hsieh, C.-C., 1986. Physical activity, all-cause mortality, and longevity of college alumni. N. Engl. J. Med. 314 (10), 605–613.
Pampel, F.C., Krueger, P.M., Denney, J.T., 2010. Socioeconomic disparities in health behaviors. Annu. Rev. Sociol. 36, 349.
Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C., Vlismas, K., Skoumas, Y., Palliou, K., et al., 2008. The effect of clinical characteristics and dietary habits on the relationship between education status and 5-year incidence of cardiovascular disease: the ATTICA study. Eur. J. Nutr. 47 (5), 258–265.

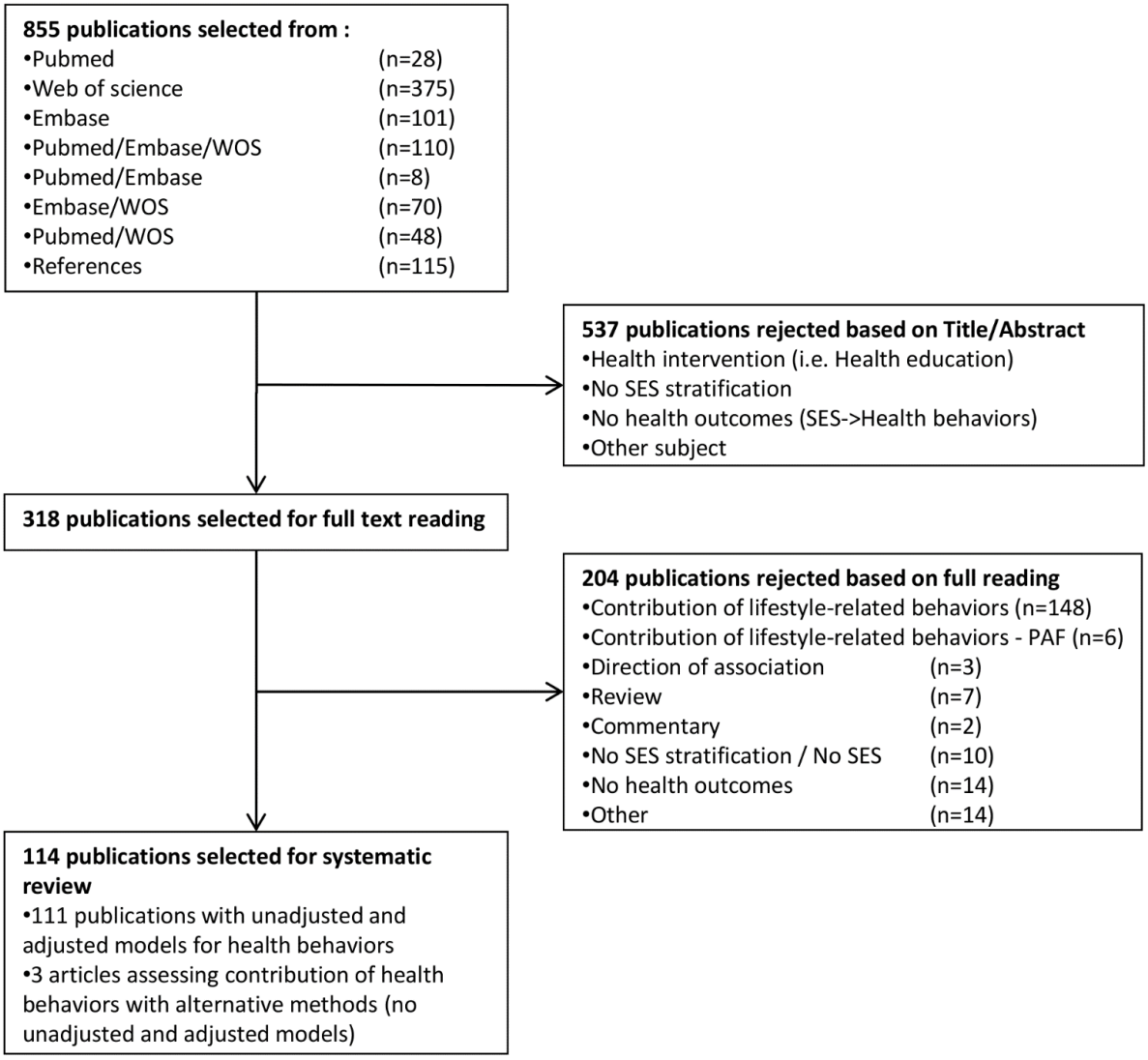
Panagiotakos, D., Georgousopoulou, E., Notara, V., Pitaraki, E., Kokkou, E., Chrysohoou, C., et al., 2015. Education status determines 10-year (2002–2012) survival from cardiovascular disease in Athens metropolitan area: the ATTICA study, Greece. Health Soc. Care Community 24, 334–344.
Pekkanen, J., Tuomilehto, J., Uutela, A., Vartiainen, E., Nissinen, A., 1995. Social class, health behaviour, and mortality among men and women in eastern Finland. BMJ 311 (7005), 589–593.
Petrovic, D., Younes, S.E., Pruijm, M., Ponte, B., Ackermann, D., Ehret, G., et al., 2016. Relation of 24-hour urinary caffeine and caffeine metabolite excretions with self-reported consumption of coffee and other caffeinated beverages in the general population. Nutr. Metab. 13 (1), 81.
Pilia, G., Chen, W.-M., Scuteri, A., Orrú, M., Albai, G., Dei, M., et al., 2006. Heritability of cardiovascular and personality traits in 6,148 Sardinians. PLoS Genet. 2 (8), e132.
Ploubidis, G.B., Mathenge, W., De Stavola, B., Grundy, E., Foster, A., Kuper, H., 2013. Socioeconomic position and later life prevalence of hypertension, diabetes and visual impairment in Nakuru, Kenya. Int. J. Public Health 58 (1), 133–141.
Poulsen, K., Andersen, L.L., 2016. Linking data on work, health and lifestyle to explain socio-occupational inequality in Danish register-based incidence of diabetes. Scand. J. Public Health 44 (4), 361–368.
Power, C., Manor, O., Fox, A.J., Fogelman, K., 1990. Health in childhood and social inequalities in health in young adults. J. R. Stat. Soc. Ser. A Stat. Soc. 17–28.
Power, C., Hyppönen, E., Davey, Smith G., 2005. Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort. Am. J. Public Health 95 (8), 1396–1402.
Prentice, A.M., 2006. The emerging epidemic of obesity in developing countries. Int. J. Epidemiol. 35 (1), 93–99.
Prescott, E., Godtfredsen, N., Osler, M., Schnohr, P., Barefoot, J., 2007. Social gradient in the metabolic syndrome not explained by psychosocial and behavioural factors: evidence from the Copenhagen City Heart Study*. Eur. J. Cardiovasc. Prev. Rehabil. 14 (3), 405–412.
Prince, S.A., Adamo, K.B., Hamel, M.E., Hardt, J., Gorber, S.C., Tremblay, M., 2008. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int. J. Behav. Nutr. Phys. Act. 5 (1), 56.
Raho, E., van Oostrom, S.H., Visser, M., Huisman, M., Zantinge, E.M., Smit, H.A., et al., 2015. Generation shifts in smoking over 20 years in two Dutch population-based cohorts aged 20–100 years. BMC Public Health 15 (1), 142.
Ramsay, S.E., Whincup, P.H., Morris, R., Lennon, L., Wannamethee, S., 2008. Is socioeconomic position related to the prevalence of metabolic syndrome? Influence of social class across the life course in a population-based study of older men. Diabetes Care 31 (12), 2380–2382.
Rathmann, W., Haastert, B., Giani, G., Koenig, W., Imhof, A., Herder, C., et al., 2006. Is inflammation a causal chain between low socioeconomic status and type 2 diabetes? Results from the KORA survey 2000. Eur. J. Epidemiol. 21 (1), 55–60.
Robertson, T., Benzeval, M., Whitley, E., Popham, F., 2015a. The role of material, psychosocial and behavioral factors in mediating the association between socioeconomic position and allostatic load (measured by cardiovascular, metabolic and inflammatory markers). Brain Behav. Immun. 45, 41–49.
Robertson, T., Benzeval, M., Whitley, E., Popham, F., 2015b. The role of material, psychosocial and behavioral factors in mediating the association between socioeconomic position and allostatic load (measured by cardiovascular, metabolic and inflammatory markers). Brain Behav. Immun. 45, 41–49.
Rose, D., Harrison, E., 2007. The European socio-economic classification: a new social class schema for comparative European research. Eur. Soc. 9 (3), 459–490.
Rosengren, A., Subramanian, S., Islam, S., Chow, C.K., Avezum, A., Kazmi, K., et al., 2009. Education and risk for acute myocardial infarction in 52 high, middle and low-income countries: INTERHEART case-control study. Heart 95 (24), 2014–2022.
Rostad, B., Schei, B., Nilsen, T.I.L., 2009. Social inequalities in mortality in older women cannot be explained by biological and health behavioural factors—results from a Norwegian health survey (the HUNT study). Scand. J. Public Health 37 (4), 401–408.
Schrecker, T., 2016. 'Neoliberal epidemics' and public health: sometimes the world is less complicated than it appears. Crit. Public Health 26 (5), 477–480.
Schreier, H.M., Chen, E., 2010. Socioeconomic status in one's childhood predicts offspring cardiovascular risk. Brain Behav. Immun. 24 (8), 1324–1331.
Schrijvers, C.T., Stronks, K., van de Mheen, H.D., Mackenbach, J.P., 1999. Explaining educational differences in mortality: the role of behavioral and material factors. Am. J. Public Health 89 (4), 535–540.
Schulz, A., House, J., Israel, B., Mentz, G., Dvonch, J., Miranda, P., et al., 2008. Relational pathways between socioeconomic position and cardiovascular risk in a multiethnic urban sample: complexities and their implications for improving health in economically disadvantaged populations. J. Epidemiol. Community Health 62 (7), 638–646.
Seligman, H.K., Jacobs, E.A., López, A., Tschann, J., Fernandez, A., 2012. Food insecurity and glycemic control among low-income patients with type 2 diabetes. Diabetes Care 35 (2), 233–238.
Shamshirgaran, S.M., Jorm, L., Bambrick, H., Hennessy, A., 2013. Independent roles of country of birth and socioeconomic status in the occurrence of type 2 diabetes. BMC Public Health 13 (1), 1.
Sharma, S., Durand, R.M., Gur-Arie, O., 1981. Identification and analysis of moderator variables. J. Mark. Res. 291–300.
Silhol, R., Zins, M., Chauvin, P., Chaix, B., 2011. Investigating the spatial variability in incidence of coronary heart disease in the Gazel cohort: the impact of area socioeconomic position and mediating role of risk factors. J. Epidemiol. Community Health 65 (2), 137–143.
Silva, L.M., Coolman, M., Steegers, E.A., Jaddoe, V.W., Moll, H.A., Hofman, A., et al., 2008. Low socioeconomic status is a risk factor for preeclampsia: the generation R study. J. Hypertens. 26 (6), 1200–1208.
Silventoinen, K., Pankow, J., Jousilahti, P., Hu, G., Tuomilehto, J., 2005. Educational inequalities in the metabolic syndrome and coronary heart disease among middle-aged men and women. Int. J. Epidemiol. 34 (2), 327–334.
Singh-Manoux, A., Nabi, H., Shipley, M., Guéguen, A., Sabia, S., Dugravot, A., et al., 2008. The role of conventional risk factors in explaining social inequalities in coronary heart disease: the relative and absolute approaches to risk. Epidimiology 19 (4), 599.
Skalická, V., Van Lenthe, F., Bambra, C., Krokstad, S., Mackenbach, J., 2009. Material, psychosocial, behavioural and biomedical factors in the explanation of relative socioeconomic inequalities in mortality: evidence from the HUNT study. Int. J. Epidemiol. dyp262.
Stamler, R., Shipley, M., Elliott, P., Dyer, A., Sans, S., Stamler, J., 1992. Higher blood pressure in adults with less education. Some explanations from INTERSALT. Hypertension 19 (3), 237–241.
Stamler, J., Elliott, P., Appel, L., Chan, Q., Buzzard, M., Dennis, B., et al., 2003. Higher blood pressure in middle-aged American adults with less education—role of multiple dietary factors: the INTERMAP study. J. Hum. Hypertens. 17 (9), 655–664.
Steptoe, A., Hamer, M., O'Donnell, K., Venuraju, S., Marmot, M.G., Lahiri, A., 2010. Socioeconomic status and subclinical coronary disease in the Whitehall II epidemiological study. PLoS One 5 (1), e8874.
Strand, B.H., Tverdal, A., 2004. Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other heart diseases? 26 year follow up of 50,000 Norwegian men and women. J. Epidemiol. Community Health 58 (8), 705–709.
Stringhini, S., Sabia, S., Shipley, M., Brunner, E., Nabi, H., Kivimaki, M., et al., 2010. Association of socioeconomic position with health behaviors and mortality. JAMA 303 (12), 1159–1166.
Stringhini, S., Dugravot, A., Shipley, M., Goldberg, M., Zins, M., Kivimäki, M., et al., 2011a. Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts. PLoS Med. 8 (2), e1000419.
Stringhini, S., Dugravot, A., Shipley, M., Goldberg, M., Zins, M., Kivimäki, M., et al., 2011b. Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts. PLoS Med. 8 (2), e1000419.
Stringhini, S., Tabak, A.G., Akbaraly, T.N., Sabia, S., Shipley, M.J., Marmot, M.G., et al., 2012a. Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study. Br. Med. J. 345.
Stringhini, S., Tabak, A.G., Akbaraly, T.N., Sabia, S., Shipley, M.J., Marmot, M.G., et al., 2012b. Contribution of Modifiable Risk Factors to Social Inequalities in Type 2 Diabetes: Prospective Whitehall II Cohort Study.
Stringhini, S., Spencer, B., Marques-Vidal, P., Waeber, G., Vollenweider, P., Paccaud, F., et al., 2012c. Age and gender differences in the social patterning of cardiovascular risk factors in Switzerland: the CoLaus study. PLoS One 7 (11), e49443.
Stringhini, S., Batty, G.D., Bovet, P., Shipley, M.J., Marmot, M.G., Kumari, M., et al., 2013a. Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study. PLoS Med. 10 (7), e1001479.
Stringhini, S., Viswanathan, B., Gedeon, J., Paccaud, F., Bovet, P., 2013b. The social transition of risk factors for cardiovascular disease in the African region: evidence from three cross-sectional surveys in the Seychelles. Int. J. Cardiol. 168 (2), 1201–1206.
Stringhini, S., Rousson, V., Viswanathan, B., Gedeon, J., Paccaud, F., Bovet, P., 2014. Association of socioeconomic status with overall and cause specific mortality in the Republic of Seychelles: results from a cohort study in the African region. PLoS One 9 (7), e102858.
Stringhini, S., Zaninotto, P., Kumari, M., Kivimäki, M., Batty, G.D., 2016. Lifecourse socioeconomic status and type 2 diabetes: the role of chronic inflammation in the English Longitudinal Study of Ageing. Sci. Rep. 6.
Stuber, J., Galea, S., Link, B.G., 2008. Smoking and the emergence of a stigmatized social status. Soc. Sci. Med. 67 (3), 420–430.
Suadicani, P., Hein, H.O., Gyntelberg, F., 1997. Strong mediators of social inequalities in risk of ischaemic heart disease: a six-year follow-up in the Copenhagen Male Study. Int. J. Epidemiol. 26 (3), 516–522.
Suadicani, P., Hein, H.O., Gyntelberg, F., 2001. Socioeconomic status and ischaemic heart disease mortality in middle-aged men: importance of the duration of follow-up. The Copenhagen male study. Int. J. Epidemiol. 30 (2), 248–255.
Tamayo, T., Claessen, H., Rückert, I.-M., Maier, W., Schunk, M., Meisinger, C., et al., 2014. Treatment pattern of type 2 diabetes differs in two German regions and with patients' socioeconomic position. PLoS One 9 (6), e99773.
Tanaka, T., Gjonça, E., Gulliford, M.C., 2012. Income, wealth and risk of diabetes among older adults: cohort study using the English longitudinal study of ageing. Eur. J. Pub. Health 22 (3), 310–317.
Thun, M., Peto, R., Boreham, J., Lopez, A.D., 2012. Stages of the cigarette epidemic on entering its second century. Tob. Control. 21 (2), 96–101.
Trichopoulou, A., Lagiou, P., 1997. Healthy traditional Mediterranean diet: an expression of culture, history, and lifestyle. Nutr. Rev. 55 (11), 383–389.
Tseng, T.-S., Lin, H.-Y., 2008. Gender and age disparity in health-related behaviors and behavioral patterns based on a National Survey of Taiwan. Int. J. Behav. Med. 15 (1), 14–20.
Van Lenthe, F.J., Gevers, E., Joung, I.M., Bosma, H., Mackenbach, J.P., 2002. Material and behavioral factors in the explanation of educational differences in incidence of acute myocardial infarction: the globe study. Ann. Epidemiol. 12 (8), 535–542.
VanderWeele, T.J., 2013. Unmeasured confounding and hazard scales: sensitivity analysis for total, direct, and indirect effects. Eur. J. Epidemiol. 28 (2), 113.
VanderWeele, T.J., 2016. Mediation analysis: a practitioner's guide. Annu. Rev. Public Health 37, 17–32.
VanderWeele, T.J., Shpitser, I., 2013. On the definition of a confounder. Ann. Stat. 41 (1),

196.
Wadsworth, M.E., 1986. Serious illness in childhood and its association with later-life achievement. In: Class and Health: Research and Longitudinal Data, pp. 50–74.
Walker, R.E., Keane, C.R., Burke, J.G., 2010. Disparities and access to healthy food in the United States: a review of food deserts literature. Health Place 16 (5), 876–884.
Wannamethee, S.G., Shaper, A.G., 1997. Socioeconomic status within social class and mortality: a prospective study in middle-aged British men. Int. J. Epidemiol. 26 (3), 532–541.
Wardle, J., Steptoe, A., 2003. Socioeconomic differences in attitudes and beliefs about healthy lifestyles. J. Epidemiol. Community Health 57 (6), 440–443.
Welch, V., Petticrew, M., Tugwell, P., Moher, D., O'Neill, J., Waters, E., et al., 2012. Guidelines and guidance-PRISMA-equity 2012 extension: reporting guidelines for systematic reviews with a focus on health equity. PLoS Med. 9 (10), 1487.
Who, J., Consultation, F.E., 2003. Diet, nutrition and the prevention of chronic diseases. World Health Organ. Tech. Rep. Ser. 916, i–viii.
Wilkinson, R.G., 1994. The epidemiological transition: from material scarcity to social disadvantage? Daedalus 61–77.
Wilkinson, R.G., Marmot, M., 2003. Social Determinants of Health: The Solid Facts: World Health Organization.
Williams, E., Tapp, R., Magliano, D., Shaw, J., Zimmet, P., Oldenburg, B., 2010. Health behaviours, socioeconomic status and diabetes incidence: the Australian diabetes obesity and lifestyle study (AusDiab). Diabetologia 53 (12), 2538–2545.
Williams, E.D., Magliano, D.J., Zimmet, P.Z., Kavanagh, A.M., Stevenson, C.E., Oldenburg, B.F., et al., 2012. Area-level socioeconomic status and incidence of abnormal glucose metabolism the Australian diabetes, obesity and lifestyle (AusDiab) study. Diabetes Care 35 (7), 1455–1461.
Woodside, J., Yarnell, J., Patterson, C., Arveiler, D., Amouyel, P., Ferrières, J., et al., 2012. Do lifestyle behaviours explain socioeconomic differences in all-cause mortality, and fatal and non-fatal cardiovascular events? Evidence from middle aged men in France and Northern Ireland in the PRIME study. Prev. Med. 54 (3), 247–253.
Woodward, M., Oliphant, J., Lowe, G., Tunstall-Pedoe, H., 2003. Contribution of contemporaneous risk factors to social inequality in coronary heart disease and all causes mortality. Prev. Med. 36 (5), 561–568.
Yan, L.L., Liu, K., Daviglus, M.L., Colangelo, L.A., Kiefe, C.I., Sidney, S., et al., 2006. Education, 15-year risk factor progression, and coronary artery calcium in young adulthood and early middle age: the coronary artery risk development in young adults study. JAMA 295 (15), 1793–1800.
Zapf, D., Dormann, C., Frese, M., 1996. Longitudinal studies in organizational stress research: a review of the literature with reference to methodological issues. J. Occup. Health Psychol. 1 (2), 145.
Zhu, S., Hu, J., McCoy, T.P., Li, G., Zhu, J., Lei, M., et al., 2015. Socioeconomic status and the prevalence of type 2 diabetes among adults in northwest China. Diabetes Educ. 41 (5), 599–608.

Supplementary material



Supplementary Figure 1: Conceptual framework representing the association between SEP, mediating factors, health outcomes and confounders (C1-3: i.e. sex, age, pre-existent diseases, genetic predisposition,…). In panel A, the crude or unadjusted model is represented with the direct association leading from SEP to health. In panel B, the model comprises mediating factors, which are thought to be located on the causal pathway between SEP and health. According to this framework, mediating factors are socially patterned (arrow A) and are at the same time associated with health (arrow B). This figure was realized with MO Power Point.



Supplementary Figure 2: Flow chart representing the selection of studies to be included in the systematic review. 740 were identified in Pubmed, Web of Science and Embase electronic databases and 115 studies were retrieved from reference lists. 537 studies were rejected based on Title/Abstract reading. 318 studies were selected for full text reading, of which 204 were rejected, yielding 114 studies to be included in the systematic review. Out of the 114 included publications in the systematic review, 111 publications included the SEP-health model unadjusted for health behaviors, and a model additionally adjusted for health behaviors, while three publications did not include these two models and assessed the contribution of health behaviors according to alternative methods. This figure was realized with MO Power Point.

Supplementary Table 1: Computed contribution by health behaviors for the association between SEP and health outcomes.

Study	Country	Stratification of analyses	Regression parameter	Attenuation by health behaviors
Notkola et al., 1985[1]	Finland		Relative risk	Childhood SEP-CVD - Unadjusted β = 1.63 (smoking: 14%)
Jacobsen et al., 1988[2]	Norway	Stratified by sex	Mean difference	M: Education-CVD - Unadjusted β = 132.1 (full: 0%) W: Education-CVD - Unadjusted β = 124.6 (full: 0%)
Jeffery et al., 1991[3]	US	Stratified by sex	Other	
Stamler R. et al., 1992[4]	International	Stratified by sex	Beta coefficient	M: Education-CVD - Unadjusted β = -1.30 (full: 47%) W: Education-CVD - Unadjusted β = -4.47 (full: 35%)
Helmert et al., 1994[5]	Germany	Stratified by sex	Odds ratio	M: SEP score-Diabetes - Unadjusted β = 1.69 (smoking: 10%) SEP score-CVD - Unadjusted β = 1.88 (smoking: -11%) W: SEP score-Diabetes - Unadjusted β = 2.82 (smoking: 24%) SEP score-CVD - Unadjusted β = 2.86 (smoking: 4%)
Gliksman M.D. et al., 1995[6]	US	Women only	Relative risk	
Pekkanen et al., 1995[7]	Finland	Stratified by sex	Hazard ratio	M: Occupation-ACM - Unadjusted β = 1.86 (smoking: 24%; full: 38%) Occupation-CVD - Unadjusted β = 1.54 (smoking: 36%; full: 54%) W: Occupation-ACM - Unadjusted β = 1.49 (smoking: -5%; full: 17%) Occupation-CVD - Unadjusted β = 1.74 (smoking: -13%; full: 9%)
Brancati et al., 1996[8]	US		Odds ratio	SEP score-Diabetes - Unadjusted β = 4.09 (full: 11%)
Lynch et al., 1996[9]	Finland	Men only	Relative risk	M: Income-ACM - Unadjusted β = 3.14 (full: 24%) Income-CVD - Unadjusted β = 2.66 (full: 38%) Income-CHD - Unadjusted β = 4.34 (full: 21%)
Suadicani et al., 1997[10]	Denmark	Men only	Relative risk	M: Occupation-CVD - Unadjusted β = 1.44 (full: 69%)
Wannamethee SG et al., 1997[11]	UK	Men only	Relative risk	M: Occupation-ACM - Unadjusted β = 1.80 (smoking: 31%; full: 43%) Occupation-CVD - Unadjusted β = 1.80 (smoking: 31%; full: 43%)
Chandola et al., 1998[12]	UK	Stratified by sex	Odds ratio	
Lantz et al., 1998[13]	US		Hazard ratio	Income-ACM - Unadjusted β = 3.22 (full: 13%)
Schrijvers et al., 1999[14]	Netherlands		Relative risk	
Hart C.L. et al., 2000[15]	UK	Stratified by sex	Hazard ratio	M: Wealth-CVD - Unadjusted β = 2.29 (smoking: 11%) W: Wealth-CVD - Unadjusted β = 2.27 (smoking: 15%)
Kilander L et al., 2001[16]	Sweden	Men only	Relative risk	M: Education-CVD - Unadjusted β = 1.67 (smoking: 25%; diet: 34%)
Suadicani P. et al., 2001[17]	Denmark	Men only	Risk ratio	M: SEP score-CHD - Unadjusted β = 1.59 (smoking: 13%; alcohol: 43%; PA: 27%)
Egeland GM et al., 2002[18]	Norway	Men only	Risk ratio	
Van Lenthe et al., 2002[19]	Netherlands		Hazard ratio	Education-CHD - Unadjusted β = 1.85 (smoking: 22%; alcohol: 19%; PA: 8%)
Aslanyan et al., 2003[20]	UK		Hazard ratio	Area-CVD - Unadjusted β = 1.06 (smoking: 0%)
Osler et al., 2003[21]	Denmark	Stratified by sex	Hazard ratio	M: Income-CVD - Unadjusted β = 1.74 (full: 7%) W: Income-CVD - Unadjusted β = 2.01 (full: -6%)
Stamler et al., 2003[22]	US		Beta coefficient	Education-CVD - Unadjusted β = -0.264 (alcohol: 2%; PA: -5%; diet: 29%)

Woodward et al., 2003[23]	UK	Stratified by sex	Hazard ratio	M: Wealth-CVD - Unadjusted β = 1.48 (smoking: 27%; alcohol: -2%; PA: 3%; full: 69%) W: Wealth-CVD - Unadjusted β = 2.64 (smoking: 31%; alcohol: 6%; full: 68%)
Agardh et al., 2004[24]	Sweden	Stratified by sex	Risk ratio	M: Occupation-Diabetes - Unadjusted β = 2.90 (smoking: 14%; PA: 10%; full: 30%) W: Occupation-Diabetes - Unadjusted β = 2.70 (smoking: 35%; PA: 4%; full: 53%)
Lawlor D.A. et al., 2004[25]	UK	Women only	Odds ratio	W: Childhood SEP-CHD - Unadjusted β = 1.35 (full: 26%)
Strand et al., 2004[26]	Norway	Stratified by sex	Relative risk	M: Education-CVD - Unadjusted β = 1.33 (smoking: 48%; PA: 0%) W: Education-CVD - Unadjusted β = 1.72 (smoking: 16%; PA: 2%)
van Oort et al., 2004[27]	Netherlands		Hazard ratio	Education-ACM - Unadjusted β = 1.66 (smoking: 10%; alcohol: 10%; PA: 17%)
Blakely et al., 2005[28]	New Zealand	Stratified by sex	Rate/prevalence ratio	M: Education-ACM - Unadjusted β = 1.31 (smoking: 17%) Education-CVD - Unadjusted β = 1.33 (smoking: 19%) W: Education-ACM - Unadjusted β = 1.42 (smoking: 10%) Education-CVD - Unadjusted β = 1.66 (smoking: 10%)
Khang et al., 2005[29]	South Korea		Risk ratio	Income-ACM - Unadjusted β = 2.33 (full: 13%)
Maty S.C. et al., 2005[30]	US		Hazard ratio	Education-Diabetes - Unadjusted β = 1.51 (full: 15%)
Power C. et al., 2005[31]	UK	Women only	Hazard ratio	W: Occupation-ACM - Unadjusted β = 1.75 (full: 35%) Occupation-CVD - Unadjusted β = 2.12 (full: 36%) Occupation-CHD - Unadjusted β = 2.74 (full: 32%) Childhood SEP-ACM (Unadjusted β = 1.19 (full: 30%; Childhood SEP-CVD (Unadjusted β = 1.37 (full 19%) Childhood SEP-CHD (Unadjusted β = 1.47 (full 18%)
Silventoinen et al., 2005[32]	Finland	Stratified by sex	Odds ratio	M: Education-MS - Unadjusted β = 0.39 (full: 10%) W: Education-MS - Unadjusted β = 0.40 (full: 13%)
van Oort et al., 2005[33]	Netherlands		Hazard ratio	Education-ACM - Unadjusted β = 2.57 (full: 17%)
Avendano et al., 2006[34]	US		Hazard ratio	
Kittleson et al., 2006 [35]	US Doctors (all age groups)		Hazard ratio	
Kittleson et al., 2006 [35]	US Doctors (<50y)		Hazard ratio	Childhood SEP-CVD - Unadjusted β = 2.40 (smoking: 7%; PA: -33%)
Rathmann et al., 2006 [36]	Germany	Stratified by sex	Odds ratio	M: SEP score-Diabetes - Unadjusted β = 1.40 (full: 13%) W: SEP score-Diabetes - Unadjusted β = 1.78 (full: 30%)
Yan et al., 2006 [37]	US		Odds ratio	Education-CVD - Unadjusted β = 4.14 (full: 32%)
Agardh et al., 2007 [38]	Sweden	Stratified by sex	Relative risk	M: W: Education-Diabetes - Unadjusted β = 2.50 (smoking: 14%; PA: 9%)
Feinglass et al., 2007[39]	US		Hazard ratio	Education-ACM - Unadjusted β = 0.79 (full: -16%) Income-ACM - Unadjusted β = 1.40 (full: 13%)
Gorman et al., 2007[40]	US		Odds ratio	Education-CVD – Unadjusted β =0.73 (full: 56%)
Kivimäki M. et al., 2007[41]	Finland	Stratified by sex	Odds ratio	M: Income-CVD - Unadjusted β = 2.24 (full: 22%) W: Income-CVD - Unadjusted β = 2.12 (full: 9%)
Kuper et al., 2007[42]	Sweden	Women only	Hazard ratio	W: Education-CVD - Unadjusted β = 2.10 (smoking: 21%; alcohol: 21%; PA: 7%)
Loucks et al., 2007[43]	US	Stratified by sex	Odds ratio	M: Education-MS - Unadjusted β = 1.33 (full: 16%) W: Education-MS - Unadjusted β = 2.25 (full: 24%)
Prescott et al., 2007 [44]	Denmark		Odds ratio	Education-MS - Unadjusted β = 0.35 (full: 8%)
Ito S et al., 2008 [45]	Japan		Hazard ratio	Education-ACM - Unadjusted β = 1.31 (full: 26%) Education-CVD - Unadjusted β = 1.53 (full: 14%)

Laaksonen et al., 2008[46]	Finland	Stratified by sex	Hazard ratio	M: Education-ACM - Unadjusted β = 1.64 (smoking: 24%; alcohol: -6%; PA: 11%; diet: 25%; full: 39%) Education-CVD - Unadjusted β = 1.46 (smoking: 27%; alcohol: -2%; PA: 13%; diet: 50%; full: 50%) W: Education-ACM - Unadjusted β = 1.32 (smoking: 20%; alcohol: -11%; PA: 8%; diet: 17%; full: 34%) Education-CVD - Unadjusted β = 2.16 (smoking: 4%; alcohol: -2%; PA: 5%; diet: 6%; full: 17%)
Laszlo et al., 2008[47]	Sweden	Women only	Hazard ratio	Income-CVD – Unadjusted β = 0.39 (smoking: 13%; alcohol: 24%)
Marmot et al., 2008[48]	UK	Men only	Hazard ratio	M: Occupation-CVD - Unadjusted β = 2.17 (smoking: 19%; full: 30%)
Maty S.C. et al., 2008 [49]	US		Hazard ratio	Childhood SEP-Diabetes - Unadjusted β = 1.60 (full: 0%)
McFadden et al., 2008[50]	UK	Stratified by sex	Relative risk	M: Occupation-ACM - Unadjusted β = 2.21 (smoking: 16%) W: Occupation-ACM - Unadjusted β = 1.64 (smoking: 6%)
Panagiotakos et al., 2008[51]	Greece		Hazard ratio	
Ramsay S.E. et al., 2008 [52]	UK	Men only	Odds ratio	
Schulz A.J. et al., 2008[53]	US		Beta coefficient	
Silva et al., 2008[54]	Netherlands	Women only	Odds ratio	W: Education-CVD - Unadjusted β = 5.12 (smoking: -15%; alcohol: 3%)
Singh-Manoux et al., 2008[55]	UK	Men only	Relative risk	M: Occupation-CVD - Unadjusted β = 1.66 (smoking: 15%)
Khang/Selmer et al., 2009[56]	South Korea		Relative risk	Education-ACM - Unadjusted β = 2.83 (full: 11%) Occupation-ACM - Unadjusted β = 1.92 (full: 12%)
McFadden et al., 2009[57]	UK		Hazard ratio	Occupation-Stroke - Unadjusted β = 2.62 (full: 3%)
Münster E et al., 2009[58]	Germany		Odds ratio	Wealth-Obesity - Unadjusted β = 2.91 (smoking: 12%)
Rosengren et al., 2009[59]	International		Odds ratio	Education-CVD - Unadjusted β = 1.56 (full: 39%) Occupation-CVD - Unadjusted β = 1.33 (full: 73%) Income-CVD - Unadjusted β = 1.28 (full: 47%) Wealth-CVD (Unadjusted β = 0.79 (full: 87%)
Rostad et al., 2009[60]	Norway	Women only	Hazard ratio	W: Education-ACM - Unadjusted β = 1.21 (full: 18%) Education-CVD - Unadjusted β = 1.21 (full: 13%)
Skalicka et al., 2009[61]	Norway		Hazard ratio	Education-ACM - Unadjusted β = 1.67 (full: 32%) Income-ACM - Unadjusted β = 2.03 (full: 14%)
Beauchamp et al., 2010[62]	Australia		Hazard ratio	Education-CVD - Unadjusted β = 1.66 (smoking: 20%; alcohol: 5%; PA: 9%; diet: 2%; full: 32%)
Chaix et al., 2010[63]	France		Beta coefficient	Education-CVD - Unadjusted β = 3.96 (full: 30%) Area-CVD - Unadjusted β = 2.39 (full: 64%)
Chapman et al., 2010[64]	US		Odds ratio	SEP score-ACM - Unadjusted β = 1.34 (full: 55%)
Kavanagh et al., 2010[65]	Australia	Stratified by sex	Beta coefficient	M: Education-Diabetes - Unadjusted β = 0.41 (full: 12%) W: Education-CVD - Unadjusted β = 4.47 (full: 26%) Income-Obesity - Unadjusted β = 3.09 (full: 36%)
Krishnan S. et al., 2010[66]	US	Women only	Risk ratio	W: Education-Diabetes - Unadjusted β = 1.28 (full: 26%) Income-Diabetes - Unadjusted β = 1.57 (full: 60%) Area-Diabetes - Unadjusted β = 1.65 (full: 54%)
Lantz et al., 2010[67]	US		Hazard ratio	Education-ACM - Unadjusted β = 1.40 (full: 43%) Income-ACM - Unadjusted β = 2.12 (full: 25%)

Manuck S.B. et al., 2010[68]	US		Odds ratio	SEP score-CVD - Unadjusted β = 0.76 (full: 14%) SEP score-Obesity - Unadjusted β = 0.74 (full: 4%)
Maty et al., 2010[69]	US White		Hazard ratio	Education-Diabetes - Unadjusted β = 1.60 (full: 0%) Childhood SEP-Diabetes - Unadjusted β = 1.60 (full: 0%)
Maty et al., 2010[69]	US Black		Hazard ratio	Education-Diabetes - Unadjusted β = 0.50 (full: 0%)
Schreier et al., 2010[70]	Canada		Beta coefficient	Education-CVD - Unadjusted β = -0.434 (smoking: 2%; PA: 1%)
Steptoe A. et al., 2010[71]	UK		Mean difference	Occupation-CVD - Unadjusted β = 0.824 (full: -7%)
Stringhini et al., 2010[72]	UK		Hazard ratio	Occupation-ACM - Unadjusted β = 1.60 (smoking: 31%; alcohol: 12%; PA: 21%; diet: 17%; full: 72%) Occupation-CVD - Unadjusted β = 3.05 (smoking: 12%; alcohol: 18%; PA: 12%; diet: 7%; full: 45%)
Williams et al., 2010[73]	Australia		Odds ratio	Education-Diabetes - Unadjusted β = 2.10 (full: 21%)
Brummett B.H. et al., 2011[74]	US		Unstandardized path weights	Income-CVD - Unadjusted β = -0.590 (smoking: 136%; alcohol: 261%; PA: 34%)
Demakakos et al., 2011[75]	UK		Hazard ratio	Education-Diabetes - Unadjusted β = 2.09 (full: 26%) Occupation-Diabetes - Unadjusted β = 1.48 (full: 47%) Income-Diabetes - Unadjusted β = 1.63 (full: 40%) Wealth-Diabetes (Unadjusted β = 2.65 (full: 22%; Childhood SEP – Diabetes Unadjusted β = 2.05 (full 20%)
Dinca et al., 2011[76]	Canada	Stratified by sex	Odds ratio	M: Education-Diabetes - Unadjusted β = 1.19 (full: 61%) Income-Diabetes - Unadjusted β = 1.90 (full: -3%) W: Education-Diabetes - Unadjusted β = 1.24 (full: 64%) Income-Diabetes - Unadjusted β = 3.24 (full: 14%)
Franks et al., 2011[77]	US		Hazard ratio	SEP score-CHD - Unadjusted β = 1.79 (smoking: 21%)
Fu C et al., 2011[78]	China		Odds ratio	
Gustafsson et al., 2011[79]	Sweden	Stratified by sex	Odds ratio	M: SEP score-MS - Unadjusted β = 1.79 (full: 47%) W: SEP score-MS - Unadjusted β = 2.05 (full: 23%)
Niedhammer et al., 2011[80]	France		Hazard ratio	Occupation-ACM - Unadjusted β = 1.88 (full: 0%)
Silhol et al., 2011[81]	France		Hazard ratio	
Stringhini et al., 2011[82]	UK-Whitehall		Hazard ratio	Occupation-ACM - Unadjusted β = 1.62 (smoking: 32%; alcohol: 13%; PA: 20%; diet: 24%; full: 75%)
Stringhini et al., 2011[82]	France-Gazel		Hazard ratio	Occupation-ACM - Unadjusted β = 1.94 (smoking: 4%; alcohol: 7%; PA: 8%; diet: 4%; full: 19%)
Dinca et al., 2012[83]	Canada		Hazard ratio	Income-Diabetes - Unadjusted β = 1.41 (full: 11%)
Hagger-Johnson et al., 2012[84]	UK		Hazard ratio	
Ploubidis et al., 2012[85]	Kenya - urban population		Beta coefficient	
f et al., 2012[85]	Kenya - rural population		Beta coefficient	
Seligman H.K. et al., 2012[86]	US		Odds ratio	Wealth-Diabetes - Unadjusted β = 1.46 (diet: 11%)
Stringhini et al., 2012[87]	UK		Hazard ratio	Occupation-Diabetes - Unadjusted β = 1.86 (smoking: 5%; alcohol: 2%; PA: 6%; diet: 8%; full: 15%)

Tanaka et al., 2012[88]	UK	Stratified by sex	Odds ratio	M: Wealth-Diabetes - Unadjusted β = 1.93 (full: 32%) W: Wealth-Diabetes - Unadjusted β = 3.15 (full: 36%) Wealth-Obesity - Unadjusted β = 2.98 (full: 3%)
Williams E.D. et al., 2012[89]	Australia		Odds ratio	Area-Diabetes - Unadjusted β = 1.53 (full: 11%)
Woodside et al., 2012[90]	France and UK		Hazard ratio	Education-ACM - Unadjusted β = 0.85 (full: 42%)
Ni et al., 2013[91]	Taiwan	Stratified by sex	Odds ratio	M: W: SEP score-MS - Unadjusted β = 0.85 (full: 7%)
Shamshirgaran et al., 2013[92]	Australia		Odds ratio	Education-Diabetes - Unadjusted β = 1.71 (full: 43%) Income-Diabetes - Unadjusted β = 1.42 (full: 12%)
Dinwiddie et al., 2014[93]	US - Foreign born US Mexicans	Stratified by sex	Odds ratio	M: Education-Diabetes - Unadjusted β = 1.22 (full: 0%) Education-CVD - Unadjusted β = 3.11 (full: -0%) Education-Obesity - Unadjusted β = 1.22 (full: -20%) W: Education-Diabetes - Unadjusted β = 0.90 (full: -43%) Education-CVD - Unadjusted β = 0.46 (full: 0%) Education-Obesity - Unadjusted β = 1.21 (full: -4%)
Dinwiddie et al., 2014[93]	US - US born US Mexicans	Stratified by sex	Odds ratio	M: Education-Diabetes - Unadjusted β = 1.13 (full: 0%) Education-CVD - Unadjusted β = 2.63 (full: -0%) Education-Obesity - Unadjusted β = 1.12 (full: -31%) W: Education-Diabetes - Unadjusted β = 0.32 (full: 3%) Education-CVD - Unadjusted β = 0.46 (full: -3%) Education-Obesity - Unadjusted β = 1.04 (full: -24%)
Giesinger et al., 2014[94]	UK		Hazard ratio	Childhood SEP-ACM - Unadjusted β = 1.97 (smoking: 50%)
Hwang J et al., 2014[95]	South Korea		Odds ratio	Education-Diabetes - Unadjusted β = 1.74 (full: 11%) Income-Diabetes - Unadjusted β = 1.37 (full: 5%)
Lear S.A. et al., 2014[96]	International		Odds ratio	Wealth-Diabetes - Unadjusted β = 1.38 (full: 19%) Wealth-Obesity - Unadjusted β = 1.43 (full: 8%)
Lipowicz et al., 2014[97]	Poland	Men only	Odds ratio	M: Education-MS - Unadjusted β = 1.30 (full: -12%) W:
Nandi et al., 2014[98]	US		Risk ratio	SEP score-ACM - Unadjusted β = 2.84 (smoking: 13%; alcohol: 17%; PA: 17%; full: 41%)
Nordahl et al., 2014[99]	Denmark	Stratified by sex	Hazard ratio	M: Education-CVD - Unadjusted β = 1.55 (smoking: 7%; PA: 1%) W: Education-CVD - Unadjusted β = 1.65 (smoking: 4%; PA: 0%)
Nordahl et al., 2014 [100]	Denmark	Stratified by sex	Rate difference in additional death per 100'000 Person-Years	M: Education-ACM - Unadjusted β = 1277 (smoking: 22%) Education-CVD - Unadjusted β = 464 (smoking: 17%) W: Education-ACM - Unadjusted β = 746 (smoking: 23%) Education-CVD - Unadjusted β = 200 (smoking: 15%)
Stringhini et al., 2014[101]	Seychelles		Hazard ratio	Occupation-ACM - Unadjusted β = 1.80 (smoking: 16%; alcohol: 12%; full: 23%) Occupation-CVD - Unadjusted β = 1.95 (smoking: 6%; alcohol: 3%; full: 10%)
Tamayo T. et al., 2014[102]	Germany		Rate/prevalence ratio	
Dupre et al., 2015[103]	US elderly (low Hba1c)		Hazard ratio	
Dupre et al., 2015[103]	US elderly (high Hba1c)		Hazard ratio	Education-ACM - Unadjusted β = 1.62 (full: 11%)
Panagiotakos et al., 2015[104]	Greece		Relative risk	Education-CVD - Unadjusted β = 1.52 (full: 13%)
Robertson et al., 2015[105]	UK		Beta coefficient	Occupation-MS - Unadjusted β = -0.450 (smoking: 33%; alcohol: 2%; PA: 4%; diet: 11%; full: 24%)
Zhu et al., 2015 [106]	China		Odds ratio	Occupation-Diabetes - Unadjusted β = 9.04 (full: -6%) Income-Diabetes - Unadjusted β = 2.89 (full: -11%)

Bihan et al., 2016 [107]	Australia		Hazard ratio	Area-ACM - Unadjusted β = 1.27 (full: -3%)
Bonaccio et al., 2016 [108]	Italy		Hazard ratio	
Deere et al., 2016 [109]	US		Odds ratio	Education-CVD - Unadjusted β = 0.67 (full:-59%); Income-CVD Unadjusted β = 0.54 (full: -16%)
Floud et al., 2016 [110]	UK	Women only	Relative risk	W: Education-CVD - Unadjusted β = 2.46 (smoking: 15%; alcohol: 13%; PA: 11%; full: 40%) Area-CVD - Unadjusted β = 1.96 (smoking: 21%; alcohol: 11%; PA: 9%; full: 45%)
Houle et al., 2016 [111]	Canada		Other	Total effect of education : -0.35**; Direct effect : -0.29*; Indirect effect (smoking) : -0.05
Montez et al., 2016 [112]	US	Women only	Hazard ratio	W: Education-MS - Unadjusted β = 1.51 (full: 7%)
Montez et al., 2016 [112]	US	Women only	Odds ratio	W: Education-MS - Unadjusted β = 1.72 (full: 30%)
Poulsen et al., 2016 [113]	Denmark		Risk ratio	Occupation-Diabetes - Unadjusted β = 1.64 (full: 68%)
Stringhini et al., 2016 [114]	UK		Hazard ratio	Education-Diabetes - Unadjusted β = 1.53 (full: 67%) Wealth-Diabetes - Unadjusted β = 1.76 (full: 61%) SEP score-ACM - Unadjusted β = 2.10 (full: 45%) Childhood SEP-Diabetes (Unadjusted β = 1.55 (full: 45%)

ACM: All-cause mortality, CVD: Cardiovascular disease (including mortality, incidence, morbidity, prevalence, stroke, coronary heart disease), MS: Metabolic syndrome (including allostatic load), PA: Physical activity, M: Men, W: Women, Full: Adjustment was performed for all previously mentioned health behaviors (Table 1) or additional covariables added simultaneously to the adjusted model (2) (BMI, hypertension,…)

β1 : β coefficient for SEP → Health outcomes unadjusted for health behaviors

Contribution percentages were computed according to the absolute scale difference method [72]

Supplementary Table 2: Contribution of health behaviors according to the assessment method of SEP indicators (Questionnaire vs. Objective assessment)

Health behavior	SEP assessment method	SEP indicator		
		Education	Occupation	Other SEP indicators
Multiple health behaviors	Questionnaire	16% [a] (-59%;67%) [b]; n=53 [c]	36% (-6%;73%); n=16	24% (-16%;69%); n=38
	Objective assessment	29% (26%;32%); n=3	35% (-7%;75%); n=12	22% (-6%;64%); n=12
Smoking	Questionnaire	17% (-15%;48%); n=25	15% (-13%;36%); n=9	16% (-11%;136%); n=14
	Objective assessment		22% (4%;33%); n=11	18% (0%;50%); n=5
Alcohol	Questionnaire	4% (-11%;21%); n=11	7% (3%;12%); n=2	50% (-2%;261%); n=7
	Objective assessment		10% (2%;18%); n=6	
Physical activity	Questionnaire	6% (-5%;17%); n=16	7% (4%;10%); n=2	10% (-33%;34%); n=6
	Objective assessment		14% (4%;21%); n=6	
Diet	Questionnaire	23% (2%;50%); n=7		
	Objective assessment		13% (4%;24%); n=6	11% (11%;11%); n=1

[a]: Median contribution
[b]: Minimum and maximum contributions for each association. Contribution percentages for each association were computed according to the absolute scale difference method [72]
[c]: Number of found associations (one study may contain several associations)

Supplementary Table 3: Median, minimum and maximum contribution of health behaviors according to the assessment method of health outcomes (Questionnaire vs. Objective assessment)

Health behavior	Health outcome assessment method	Health outcome		
		All-cause mortality	Cardiovascular disorders	Metabolic disorders
Multiple health behaviors	Questionnaire	16% [a] (-59%;67%) [b]; n=53 [c]	36% (-6%;73%); n=16	24% (-16%;69%); n=38
	Objective assessment	29% (26%;32%); n=3	35% (-7%;75%); n=12	22% (-6%;64%); n=12
Smoking	Questionnaire	17% (-15%;48%); n=25	15% (-13%;36%); n=9	16% (-11%;136%); n=14
	Objective assessment		22% (4%;33%); n=11	18% (0%;50%); n=5
Alcohol	Questionnaire	4% (-11%;21%); n=11	7% (3%;12%); n=2	50% (-2%;261%); n=7
	Objective assessment		10% (2%;18%); n=6	
Physical activity	Questionnaire	6% (-5%;17%); n=16	7% (4%;10%); n=2	10% (-33%;34%); n=6
	Objective assessment		14% (4%;21%); n=6	
Diet	Questionnaire	23% (2%;50%); n=7		
	Objective assessment		13% (4%;24%); n=6	11% (11%;11%); n=1

[a]: Median contribution
[b]: Minimum and maximum contributions for each association. Contribution percentages for each association were computed according to the absolute scale difference method [72]
[c]: Number of found associations (one study may contain several associations)

Search algorithms for Pubmed, Embase, Web of Science

Pubmed

("cardiovascular disease"[Title/Abstract] OR diabetes[Title/Abstract] OR cardiometabolic [Title/Abstract] OR stroke [Title/Abstract] OR "blood sugar"[Title/Abstract] OR "heart disease"[Title/Abstract] OR coronary[Title/Abstract] OR "metabolic syndrome"[Title/Abstract] OR "myocardial infarction"[Title/Abstract] OR "infarction"[Title/Abstract] OR "blood pressure"[Title/Abstract] OR "hypertension"[Title/Abstract] OR "cardiovascular"[Title/Abstract] OR "all-cause mortality"[Title/Abstract] OR "all cause mortality"[Title/Abstract])
AND ("socioeconomic status"[Title] OR income[Title] OR education[Title] OR occupation[Title] OR "occupational position"[Title] OR "socioeconomic position"[Title] OR "occupational inequalities"[Title] OR "social disparities" [Title] OR "social inequalities" [Title] OR "health inequalities" [Title])
AND (contribut* OR mediat* OR attenuat* OR explain* OR explanation OR reduc* OR role)
AND ("lifestyle behaviors"[Title/Abstract] OR smoking[Title/Abstract] OR alcohol[Title/Abstract] OR drinking[Title/Abstract] OR diet[Title/Abstract] OR "lifestyle behaviours"[Title/Abstract] OR "lifestyle factors"[Title/Abstract] OR lifestyle[Title/Abstract] OR "health behaviours"[Title/Abstract])
NOT ("cochrane review"[Title] OR "systematic review"[Title] OR "meta analysis"[Title])
NOT (cancer[Title] OR depression[Title] OR respiratory[Title] OR "health education"[Title/Abstract] OR COPD[Title] OR pulmonary[Title] OR CRP[Title] OR "health intervention"[Title/Abstract] OR "education program"[Title/Abstract] OR "lifestyle intervention"[Title] OR "patient education"[Title/Abstract] OR dementia[Title] OR neurolog*[Title])
Restrict to

- Free full text
- English/French
- Humans

EMBASE

Login through institution on https://www.embase.com/#quickSearch/default

('cardiovascular disease':ab,ti OR diabetes:ab,ti OR 'cardiometabolic':ab,ti OR 'stroke':ab,ti OR 'blood sugar':ab,ti OR 'heart disease':ab,ti OR coronary:ab,ti OR 'metabolic syndrome':ab,ti OR 'myocardial infarction':ab,ti OR 'infarction':ab,ti OR 'blood pressure':ab,ti OR 'hypertension':ab,ti OR 'cardiovascular':ab,ti OR 'all-cause mortality':ab,ti OR 'all cause mortality':ab,ti)
AND ('socioeconomic status':ti OR income:ti OR education:ti OR occupation:ti OR 'occupational position':ti OR 'socioeconomic position':ti OR 'occupational inequalities':ti OR 'social disparities':ti OR 'social inequalities':ti OR 'health inequalities':ti)
AND (contribut* OR mediat* OR attenuat* OR explain* OR explanation OR reduc* OR role)
AND ('lifestyle behaviors':ab,ti OR smoking:ab,ti OR alcohol:ab,ti OR drinking:ab,ti OR diet:ab,ti OR 'lifestyle behaviours':ab,ti OR 'lifestyle factors':ab,ti OR lifestyle:ab,ti OR 'health behaviours':ab,ti)
AND [article]/lim NOT ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([english]/lim OR [french]/lim) AND ([male]/lim OR [female]/lim)
AND [humans]/lim
AND [abstracts]/lim
AND [<1966-2016]/py
NOT (cancer:ti OR depression:ti OR respiratory:ti OR 'health education':ab,ti OR COPD:ti OR pulmonary:ti OR CRP:ti OR 'health intervention':ab,ti OR 'education program':ab,ti OR 'lifestyle intervention':ti OR 'patient education':ab,ti OR 'dementia':ti OR neurolog*:ti)

Web of science
http://apps.webofknowledge.com/
UNDER TOPIC
AND ('lifestyle behaviors' OR smoking OR alcohol OR drinking OR diet OR 'lifestyle behaviours' OR 'lifestyle factors' OR lifestyle OR 'health behaviours')
AND (contribut* OR mediat* OR attenuat* OR explain* OR explanation OR reduc* OR role)
UNDER TITLE: **AND**
('cardiovascular disease' OR diabetes OR cardiometabolic OR stroke OR 'blood sugar' OR 'heart disease' OR coronary OR 'metabolic syndrome' OR 'myocardial infarction' OR 'infarction' OR 'blood pressure' OR 'hypertension' OR cardiovascular OR 'all-cause mortality' OR 'all cause mortality')
('socioeconomic status' OR income OR education OR occupation OR 'occupational position' OR 'socioeconomic position' OR 'occupational inequalities' OR 'social disparities' OR 'social inequalities' OR 'health inequalities')
UNDER TITLE: **NOT**
(cancer OR depression OR respiratory OR 'health education' OR COPD OR pulmonary OR CRP OR 'health intervention' OR 'education program' OR 'lifestyle intervention' OR 'patient education' OR dementia OR neurolog* OR 'cochrane review' OR 'systematic review' OR 'meta analysis' OR 'lifestyle education')
Other filters [Left menu, click Refine]: English/French ; Articles

References

1. Notkola, V., et al., *Socio-economic conditions in childhood and mortality and morbidity caused by coronary heart disease in adulthood in rural Finland.* Social science & medicine, 1985. **21**(5): p. 517-523.
2. Jacobsen, B.K. and D.S. Thelle, *Risk factors for coronary heart disease and level of education the tromsø heart study.* American Journal of Epidemiology, 1988. **127**(5): p. 923-932.
3. Jeffery, R.W., et al., *Socioeconomic status differences in health behaviors related to obesity: the Healthy Worker Project.* International journal of obesity, 1991. **15**(10): p. 689-696.
4. Stamler, R., et al., *Higher blood pressure in adults with less education. Some explanations from INTERSALT.* Hypertension, 1992. **19**(3): p. 237-241.
5. Helmert, U. and S. Shea, *Social inequalities and health status in Western Germany.* Public health, 1994. **108**(5): p. 341-356.
6. Gliksman, M.D., et al., *Childhood socioeconomic status and risk of cardiovascular disease in middle aged US women: a prospective study.* Journal of Epidemiology and Community Health, 1995. **49**(1): p. 10-15.
7. Pekkanen, J., et al., *Social class, health behaviour, and mortality among men and women in eastern Finland.* Bmj, 1995. **311**(7005): p. 589-593.
8. Brancati, F.L., et al., *Diabetes mellitus, race, and socioeconomic status a population-based study.* Annals of epidemiology, 1996. **6**(1): p. 67-73.
9. Lynch, J.W., et al., *Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction?* American journal of epidemiology, 1996. **144**(10): p. 934-942.
10. Suadicani, P., H.O. Hein, and F. Gyntelberg, *Strong mediators of social inequalities in risk of ischaemic heart disease: a six-year follow-up in the Copenhagen Male Study.* International Journal of Epidemiology, 1997. **26**(3): p. 516-522.
11. Wannamethee, S.G. and A.G. Shaper, *Socioeconomic status within social class and mortality: a prospective study in middle-aged British men.* International Journal of Epidemiology, 1997. **26**(3): p. 532-541.
12. Chandola, T., *Social inequality in coronary heart disease: a comparison of occupational classifications.* Social science & medicine, 1998. **47**(4): p. 525-533.
13. Lantz, P.M., et al., *Socioeconomic factors, health behaviors, and mortality: results from a nationally representative prospective study of US adults.* Jama, 1998. **279**(21): p. 1703-1708.
14. Schrijvers, C.T., et al., *Explaining educational differences in mortality: the role of behavioral and material factors.* American Journal of Public Health, 1999. **89**(4): p. 535-540.
15. Hart, C.L., D.J. Hole, and G.D. Smith, *The contribution of risk factors to stroke differentials, by socioeconomic position in adulthood: the Renfrew/Paisley Study.* American Journal of Public Health, 2000. **90**(11): p. 1788.
16. Kilander, L., et al., *Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men.* International Journal of Epidemiology, 2001. **30**(5): p. 1119-1126.
17. Suadicani, P., H.O. Hein, and F. Gyntelberg, *Socioeconomic status and ischaemic heart disease mortality in middle-aged men: importance of the duration of follow-up. The Copenhagen Male Study.* International journal of epidemiology, 2001. **30**(2): p. 248-255.
18. Egeland, G.M., et al., *A man's heart and a wife's education: A 12-year coronary heart disease mortality follow-up in Norwegian men.* International Journal of Epidemiology, 2002. **31**(4): p. 799-805.
19. Van Lenthe, F.J., et al., *Material and behavioral factors in the explanation of educational differences in incidence of acute myocardial infarction: the Globe study.* Annals of epidemiology, 2002. **12**(8): p. 535-542.

20. Aslanyan, S., et al., *Effect of area-based deprivation on the severity, subtype, and outcome of ischemic stroke.* Stroke, 2003. **34**(11): p. 2623-2628.
21. Osler, M., et al., *Income inequality and ischaemic heart disease in Danish men and women.* International Journal of Epidemiology, 2003. **32**(3): p. 375-380.
22. Stamler, J., et al., *Higher blood pressure in middle-aged American adults with less education—role of multiple dietary factors: the INTERMAP study.* Journal of human hypertension, 2003. **17**(9): p. 655-664.
23. Woodward, M., et al., *Contribution of contemporaneous risk factors to social inequality in coronary heart disease and all causes mortality.* Preventive medicine, 2003. **36**(5): p. 561-568.
24. Agardh, E.E., et al., *Explanations of socioeconomic differences in excess risk of type 2 diabetes in Swedish men and women.* Diabetes care, 2004. **27**(3): p. 716-721.
25. Lawlor, D.A., G.D. Smith, and S. Ebrahim, *Association between childhood socioeconomic status and coronary heart disease risk among postmenopausal women: findings from the British Women's Heart and Health Study.* American Journal of Public Health, 2004. **94**(8): p. 1386-1392.
26. Strand, B.H. and A. Tverdal, *Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other heart diseases? 26 year follow up of 50 000 Norwegian men and women.* Journal of Epidemiology and Community Health, 2004. **58**(8): p. 705-709.
27. van Oort, F.V., F.J. van Lenthe, and J.P. Mackenbach, *Cooccurrence of lifestyle risk factors and the explanation of education inequalities in mortality: results from the GLOBE study.* Preventive Medicine, 2004. **39**(6): p. 1126-1134.
28. Blakely, T. and N. Wilson, *The contribution of smoking to inequalities in mortality by education varies over time and by sex: two national cohort studies, 1981–84 and 1996–99.* International journal of epidemiology, 2005. **34**(5): p. 1054-1062.
29. Khang, Y.-H. and H.R. Kim, *Explaining socioeconomic inequality in mortality among South Koreans: an examination of multiple pathways in a nationally representative longitudinal study.* International Journal of Epidemiology, 2005. **34**(3): p. 630-637.
30. Maty, S.C., et al., *Education, income, occupation, and the 34-year incidence (1965–99) of type 2 diabetes in the Alameda County Study.* International Journal of Epidemiology, 2005. **34**(6): p. 1274-1281.
31. Power, C., E. Hyppönen, and G. Davey Smith, *Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort.* American Journal of Public Health, 2005. **95**(8): p. 1396-1402.
32. Silventoinen, K., et al., *Educational inequalities in the metabolic syndrome and coronary heart disease among middle-aged men and women.* International Journal of Epidemiology, 2005. **34**(2): p. 327-334.
33. van Oort, F.V., F.J. van Lenthe, and J.P. Mackenbach, *Material, psychosocial, and behavioural factors in the explanation of educational inequalities in mortality in The Netherlands.* Journal of Epidemiology and Community Health, 2005. **59**(3): p. 214-220.
34. Avendano, M., et al., *Socioeconomic Status and Stroke Incidence in the US Elderly The Role of Risk Factors in the EPESE Study.* Stroke, 2006. **37**(6): p. 1368-1373.
35. Kittleson, M.M., et al., *Association of childhood socioeconomic status with subsequent coronary heart disease in physicians.* Archives of Internal Medicine, 2006. **166**(21): p. 2356-2361.
36. Rathmann, W., et al., *Is inflammation a causal chain between low socioeconomic status and type 2 diabetes? Results from the KORA Survey 2000.* European journal of epidemiology, 2006. **21**(1): p. 55-60.
37. Yan, L.L., et al., *Education, 15-year risk factor progression, and coronary artery calcium in young adulthood and early middle age: the Coronary Artery Risk Development in Young Adults study.* Jama, 2006. **295**(15): p. 1793-1800.

38. Agardh, E., et al., *Socio-economic position at three points in life in association with type 2 diabetes and impaired glucose tolerance in middle-aged Swedish men and women.* International journal of epidemiology, 2007. **36**(1): p. 84-92.
39. Feinglass, J., et al., *Baseline health, socioeconomic status, and 10-year mortality among older middle-aged Americans: Findings from the Health and Retirement Study, 1992–2002.* The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 2007. **62**(4): p. S209-S217.
40. Gorman, B.K. and A. Sivaganesan, *The role of social support and integration for understanding socioeconomic disparities in self-rated health and hypertension.* Social science & medicine, 2007. **65**(5): p. 958-975.
41. Kivimäki, M., et al., *Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish Public Sector study.* American journal of public health, 2007. **97**(5): p. 874-879.
42. Kuper, H., et al., *The socioeconomic gradient in the incidence of stroke a prospective study in middle-aged women in Sweden.* Stroke, 2007. **38**(1): p. 27-33.
43. Loucks, E.B., et al., *Socioeconomic disparities in metabolic syndrome differ by gender: evidence from NHANES III.* Annals of epidemiology, 2007. **17**(1): p. 19-26.
44. Prescott, E., et al., *Social gradient in the metabolic syndrome not explained by psychosocial and behavioural factors: evidence from the Copenhagen City Heart Study∗.* European Journal of Cardiovascular Prevention & Rehabilitation, 2007. **14**(3): p. 405-412.
45. Ito, S., et al., *Education in relation to incidence of and mortality from cancer and cardiovascular disease in Japan.* The European Journal of Public Health, 2008. **18**(5): p. 466-472.
46. Laaksonen, M., et al., *Health behaviours as explanations for educational level differences in cardiovascular and all-cause mortality: a follow-up of 60 000 men and women over 23 years.* The European Journal of Public Health, 2008. **18**(1): p. 38-43.
47. László, K.D., I. Janszky, and S. Ahnve, *Income and recurrent events after a coronary event in women.* European journal of epidemiology, 2008. **23**(10): p. 669-680.
48. Marmot, M., et al., *Biological and behavioural explanations of social inequalities in coronary heart disease: the Whitehall II study.* Diabetologia, 2008. **51**(11): p. 1980-1988.
49. Maty, S.C., et al., *Childhood socioeconomic position, gender, adult body mass index, and incidence of type 2 diabetes mellitus over 34 years in the Alameda County Study.* American Journal of Public Health, 2008. **98**(8): p. 1486-1494.
50. McFadden, E., et al., *Occupational social class, educational level, smoking and body mass index, and cause-specific mortality in men and women: a prospective study in the European Prospective Investigation of Cancer and Nutrition in Norfolk (EPIC-Norfolk) cohort.* European journal of epidemiology, 2008. **23**(8): p. 511-522.
51. Panagiotakos, D.B., et al., *The effect of clinical characteristics and dietary habits on the relationship between education status and 5-year incidence of cardiovascular disease: the ATTICA study.* European journal of nutrition, 2008. **47**(5): p. 258-265.
52. Ramsay, S.E., et al., *Is socioeconomic position related to the prevalence of metabolic syndrome? Influence of social class across the life course in a population-based study of older men.* Diabetes care, 2008. **31**(12): p. 2380-2382.
53. Schulz, A., et al., *Relational pathways between socioeconomic position and cardiovascular risk in a multiethnic urban sample: complexities and their implications for improving health in economically disadvantaged populations.* Journal of epidemiology and community health, 2008. **62**(7): p. 638-646.
54. Silva, L.M., et al., *Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study.* Journal of hypertension, 2008. **26**(6): p. 1200-1208.
55. Singh-Manoux, A., et al., *The role of conventional risk factors in explaining social inequalities in coronary heart disease: the relative and absolute approaches to risk.* Epidemiology (Cambridge, Mass.), 2008. **19**(4): p. 599.

56. Khang, Y.H., et al., *The contribution of material, psychosocial, and behavioral factors in explaining educational and occupational mortality inequalities in a nationally representative sample of South Koreans: relative and absolute perspectives.* Soc Sci Med, 2009. **68**(5): p. 858-66.
57. McFadden, E., et al., *Social class, risk factors, and stroke incidence in men and women a prospective study in the European prospective investigation into cancer in Norfolk cohort.* Stroke, 2009. **40**(4): p. 1070-1077.
58. Münster, E., et al., *Over-indebtedness as a marker of socioeconomic status and its association with obesity: a cross-sectional study.* BMC Public Health, 2009. **9**(1): p. 1.
59. Rosengren, A., et al., *Education and risk for acute myocardial infarction in 52 high, middle and low-income countries: INTERHEART case-control study.* Heart, 2009. **95**(24): p. 2014-2022.
60. Rostad, B., B. Schei, and T.I.L. Nilsen, *Social inequalities in mortality in older women cannot be explained by biological and health behavioural factors—Results from a Norwegian health survey (the HUNT Study).* Scandinavian journal of public health, 2009. **37**(4): p. 401-408.
61. Skalická, V., et al., *Material, psychosocial, behavioural and biomedical factors in the explanation of relative socio-economic inequalities in mortality: evidence from the HUNT study.* International journal of epidemiology, 2009: p. dyp262.
62. Beauchamp, A., et al., *Inequalities in cardiovascular disease mortality: the role of behavioural, physiological and social risk factors.* Journal of epidemiology and community health, 2010. **64**(6): p. 542-548.
63. Chaix, B., et al., *Individual/neighborhood social factors and blood pressure in the RECORD cohort study which risk factors explain the associations?* Hypertension, 2010. **55**(3): p. 769-775.
64. Chapman, B.P., et al., *Personality, socioeconomic status, and all-cause mortality in the United States.* American Journal of Epidemiology, 2010. **171**(1): p. 83-92.
65. Kavanagh, A., et al., *Socioeconomic position, gender, health behaviours and biomarkers of cardiovascular disease and diabetes.* Social science & medicine, 2010. **71**(6): p. 1150-1160.
66. Krishnan, S., et al., *Socioeconomic status and incidence of type 2 diabetes: results from the Black Women's Health Study.* American Journal of Epidemiology, 2010: p. kwp443.
67. Lantz, P.M., et al., *Socioeconomic and behavioral risk factors for mortality in a national 19-year prospective study of US adults.* Social science & medicine, 2010. **70**(10): p. 1558-1566.
68. Manuck, S.B., et al., *Subjective socioeconomic status and presence of the metabolic syndrome in midlife community volunteers.* Psychosomatic medicine, 2010. **72**(1): p. 35.
69. Maty, S.C., S.A. James, and G.A. Kaplan, *Life-course socioeconomic position and incidence of diabetes mellitus among blacks and whites: the Alameda County Study, 1965-1999.* American Journal of Public Health, 2010. **100**(1): p. 137-145.
70. Schreier, H.M. and E. Chen, *Socioeconomic status in one's childhood predicts offspring cardiovascular risk.* Brain, behavior, and immunity, 2010. **24**(8): p. 1324-1331.
71. Steptoe, A., et al., *Socioeconomic status and subclinical coronary disease in the Whitehall II epidemiological study.* PLoS One, 2010. **5**(1): p. e8874.
72. Stringhini, S., et al., *Association of socioeconomic position with health behaviors and mortality.* Jama, 2010. **303**(12): p. 1159-1166.
73. Williams, E., et al., *Health behaviours, socioeconomic status and diabetes incidence: the Australian Diabetes Obesity and Lifestyle Study (AusDiab).* Diabetologia, 2010. **53**(12): p. 2538-2545.
74. Brummett, B.H., et al., *Systolic blood pressure, socioeconomic status, and biobehavioral risk factors in a nationally representative US young adult sample.* Hypertension, 2011. **58**(2): p. 161-166.
75. Demakakos, P., M. Marmot, and A. Steptoe, *Socioeconomic position and the incidence of type 2 diabetes: the ELSA study.* European journal of epidemiology, 2012. **27**(5): p. 367-378.
76. Dinca-Panaitescu, S., et al., *Diabetes prevalence and income: results of the Canadian Community Health Survey.* Health Policy, 2011. **99**(2): p. 116-123.

77. Franks, P., et al., *Do changes in traditional coronary heart disease risk factors over time explain the association between socio-economic status and coronary heart disease?* BMC cardiovascular disorders, 2011. **11**(1): p. 1.
78. Fu, C., et al., *High prevalence of hyperglycaemia and the impact of high household income in transforming Rural China.* BMC public health, 2011. **11**(1): p. 1.
79. Gustafsson, P.E., M. Persson, and A. Hammarstrom, *Life Course Origins of the Metabolic Syndrome in Middle-Aged Women and Men: The Role of Socioeconomic Status and Metabolic Risk Factors in Adolescence and Early Adulthood.* Annals of Epidemiology, 2011. **21**(2): p. 103-110.
80. Niedhammer, I., et al., *Occupational and behavioural factors in the explanation of social inequalities in premature and total mortality: a 12.5-year follow-up in the Lorhandicap study.* European journal of Epidemiology, 2011. **26**(1): p. 1-12.
81. Silhol, R., et al., *Investigating the spatial variability in incidence of coronary heart disease in the Gazel cohort: the impact of area socioeconomic position and mediating role of risk factors.* Journal of epidemiology and community health, 2011. **65**(2): p. 137-143.
82. Stringhini, S., et al., *Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts.* PLoS medicine, 2011. **8**(2): p. e1000419.
83. Dinca-Panaitescu, M., et al., *The dynamics of the relationship between diabetes incidence and low income: Longitudinal results from Canada's National Population Health Survey.* Maturitas, 2012. **72**(3): p. 229-235.
84. Hagger-Johnson, G., et al., *Neuroticism and cardiovascular disease mortality: socioeconomic status modifies the risk in women (UK Health and Lifestyle Survey).* Psychosomatic medicine, 2012. **74**(6): p. 596-603.
85. Ploubidis, G.B., et al., *Socioeconomic position and later life prevalence of hypertension, diabetes and visual impairment in Nakuru, Kenya.* International journal of public health, 2013. **58**(1): p. 133-141.
86. Seligman, H.K., et al., *Food insecurity and glycemic control among low-income patients with type 2 diabetes.* Diabetes Care, 2012. **35**(2): p. 233-238.
87. Stringhini, S., et al., *Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study.* 2012.
88. Tanaka, T., E. Gjonça, and M.C. Gulliford, *Income, wealth and risk of diabetes among older adults: cohort study using the English longitudinal study of ageing.* The European Journal of Public Health, 2012. **22**(3): p. 310-317.
89. Williams, E.D., et al., *Area-level socioeconomic status and incidence of abnormal glucose metabolism the Australian Diabetes, Obesity and Lifestyle (AusDiab) study.* Diabetes Care, 2012. **35**(7): p. 1455-1461.
90. Woodside, J., et al., *Do lifestyle behaviours explain socioeconomic differences in all-cause mortality, and fatal and non-fatal cardiovascular events? Evidence from middle aged men in France and Northern Ireland in the PRIME Study.* Preventive medicine, 2012. **54**(3): p. 247-253.
91. Ni, L.F., et al., *Substance use, gender, socioeconomic status and metabolic syndrome among adults in Taiwan.* Public Health Nursing, 2013. **30**(1): p. 18-28.
92. Shamshirgaran, S.M., et al., *Independent roles of country of birth and socioeconomic status in the occurrence of type 2 diabetes.* BMC public health, 2013. **13**(1): p. 1.
93. Dinwiddie, G.Y., R.E. Zambrana, and M.A. Garza, *Exploring risk factors in Latino cardiovascular disease: the role of education, nativity, and gender.* American journal of public health, 2014. **104**(9): p. 1742-1750.
94. Giesinger, I., et al., *Association of socioeconomic position with smoking and mortality: the contribution of early life circumstances in the 1946 birth cohort.* Journal of epidemiology and community health, 2013: p. jech-2013-203159.

95. Hwang, J. and C. Shon, *Relationship between socioeconomic status and type 2 diabetes: results from Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2012.* BMJ open, 2014. **4**(8): p. e005710.
96. Lear, S.A., et al., *The association between ownership of common household devices and obesity and diabetes in high, middle and low income countries.* Canadian Medical Association Journal, 2014. **186**(4): p. 258-266.
97. Lipowicz, A., A. Szklarska, and R.M. Malina, *Allostatic load and socioeconomic status in Polish adult men.* Journal of biosocial science, 2014. **46**(02): p. 155-167.
98. Nandi, A., M.M. Glymour, and S. Subramanian, *Association among socioeconomic status, health behaviors, and all-cause mortality in the United States.* Epidemiology, 2014. **25**(2): p. 170-177.
99. Nordahl, H., et al., *Education and risk of coronary heart disease: assessment of mediation by behavioral risk factors using the additive hazards model (vol 28, pg 149, 2013).* European Journal of Epidemiology, 2014. **29**(4): p. 303-306.
100. Nordahl, H., et al., *Education and cause-specific mortality: the mediating role of differential exposure and vulnerability to behavioral risk factors.* Epidemiology, 2014. **25**(3): p. 389-396.
101. Stringhini, S., et al., *Association of socioeconomic status with overall and cause specific mortality in the Republic of Seychelles: results from a cohort study in the african region.* PloS one, 2014. **9**(7): p. e102858.
102. Tamayo, T., et al., *Treatment pattern of type 2 diabetes differs in two German regions and with patients' socioeconomic position.* PloS one, 2014. **9**(6): p. e99773.
103. Dupre, M.E., et al., *Education, glucose control, and mortality risks among US older adults with diabetes.* Diabetes research and clinical practice, 2015. **107**(3): p. 392-399.
104. Panagiotakos, D., et al., *Education status determines 10-year (2002–2012) survival from cardiovascular disease in Athens metropolitan area: the ATTICA study, Greece.* Health & social care in the community, 2015.
105. Robertson, T., et al., *The role of material, psychosocial and behavioral factors in mediating the association between socioeconomic position and allostatic load (measured by cardiovascular, metabolic and inflammatory markers).* Brain, behavior, and immunity, 2015. **45**: p. 41-49.
106. Zhu, S., et al., *Socioeconomic status and the prevalence of type 2 diabetes among adults in northwest China.* The Diabetes Educator, 2015. **41**(5): p. 599-608.
107. Bihan, H., et al., *Socioeconomic position and premature mortality in the AusDiab cohort of australian adults.* American Journal of Public Health, 2016. **106**(3): p. 470-477.
108. Bonaccio, M., et al., *Interaction between education and income on the risk of all-cause mortality: prospective results from the MOLI-SANI study.* International journal of public health, 2016: p. 1-12.
109. Bradley Deere, M. and M. Seth Lirette, *Life Course Socioeconomic Position and Subclinical Disease: The Jackson Heart Study.* Ethnicity & Disease, 2016. **26**(3): p. 355.
110. Floud, S., et al., *The role of health-related behavioural factors in accounting for inequalities in coronary heart disease risk by education and area deprivation: prospective study of 1.2 million UK women.* BMC medicine, 2016. **14**(1): p. 145.
111. Houle, J., et al., *Socioeconomic status and glycemic control in adult patients with type 2 diabetes: a mediation analysis.* BMJ open diabetes research & care, 2016. **4**(1): p. e000184.
112. Montez, J.K., et al., *Life-course Socioeconomic Status and Metabolic Syndrome Among Midlife Women.* The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 2016: p. gbw014.
113. Poulsen, K. and L.L. Andersen, *Linking data on work, health and lifestyle to explain socio-occupational inequality in Danish register-based incidence of diabetes.* Scandinavian journal of public health, 2016. **44**(4): p. 361-368.
114. Stringhini, S., et al., *Lifecourse socioeconomic status and type 2 diabetes: the role of chronic inflammation in the English Longitudinal Study of Ageing.* Scientific reports, 2016. **6**.

Chapter 2 The contribution of sleep to social inequalities in cardiovascular disorders: a multi-cohort study

The contribution of sleep to social inequalities in cardiovascular disorders: a multi-cohort study

Dusan Petrovic[1], José Haba-Rubio[2], Carlos de Mestral Vargas[1], Michelle Kelly-Irving[3,4], Paolo Vineis[5], Mika Kivimäki[6], Solja Nyberg[7], Martina Gandini[8], Murielle Bochud[1], Peter Vollenweider[1], Angelo d'Errico[8], Henrique Barros[9], Silvia Fraga[9], Marcel Goldberg[10,11], Marie Zins[10,11], Andrew Steptoe[6], Cyrille Delpierre[3,4], Raphael Heinzer[2], **Cristian Carmeli[1*], Marc Chadeau-Hyam[5*], and Silvia Stringhini[1, 12*]**, for the Lifepath consortium[13]

1. Institute of Social and Preventive Medicine (IUMSP), Centre universitaire de médecine Générale et santé publique (UNISANTÉ), Lausanne, Switzerland
2. Center for Investigation and Research in Sleep, Lausanne University Hospital, Lausanne, Switzerland
3. INSERM, UMR 1027, Toulouse, France
4. Université Toulouse III Paul-Sabatier, UMR1027, Toulouse, France
5. Centre for Environment and Health, School of Public Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK
6. Department of Epidemiology and Public Health, University College London, London, UK
7. Clinicum, Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland
8. Epidemiology Unit, ASL TO3 Piedmont Region, Grugliasco, Italy
9. EPIUnit-Institute of Public Health, University of Porto, Porto, Portugal
10. Population-based Epidemiological Cohorts Unit, INSERM UMS 11, Villejuif, France
11. Paris Descartes University, Paris, France
12. Unit of Population Epidemiology, Primary Care Division, Geneva University Hospital, Geneva, Switzerland
13. Members are listed at the end of the paper

*** Senior authors**

Correspondence:
Dr. Silvia Stringhini, e-mail: silvia.stringhini@unisante.ch
Address: Route de la Corniche 10, 1010 Lausanne, Switzerland
Telephone: +41 (0)21 314 26 14
FAX: +41 (0)21 314 73 73

Key words: socioeconomic position, life-course, sleep duration, mediation, cardiovascular disorders

Abstract: 301
Words: 6919 (Abstract, Manuscript text, References, Figure legends)
References: 53
Tables: 4
Figures: 1

Abstract

Aims

Sleep disturbances exhibit a strong social patterning, and inadequate sleep has been associated with adverse health outcomes, including cardiovascular disorders (CVD). However, the contribution of sleep to socioeconomic inequalities in CVD is unclear. This study pools data from eight European cohorts to investigate the role of sleep duration in the association between life-course socioeconomic position (SEP) and CVD.

Methods and Results

We used cross-sectional data from eight European cohorts, totaling 111,205 participants. Life-course SEP was assessed using father's and adult occupational position. Self-reported sleep duration was categorized into recommended (6h-8.5h/night), long (>8.5h/night), and short (<6h/night). We examined two cardiovascular outcomes: coronary heart disease (CHD) and stroke. Main analyses were conducted using pooled data and examined the association between life-course SEP and CVD, and the contribution of sleep duration to this gradient using counterfactual mediation. Low father's occupational position was associated with an increased risk of CHD (men: OR=1.19, 95% CI [1.04;1.37]; women: OR=1.25, 95% CI [1.02;1.54]), with marginal decrease of the gradient after accounting for adult occupational position (men: OR=1.17, 95% CI [1.02;1.35]; women: OR=1.22, 95% CI [0.99;1.52]), and no mediating effect by short sleep duration. Low adult occupational position was associated with an increased risk of CHD in both men and women (men: OR=1.48, 95% CI [1.14;1.92]; women: OR=1.53, 95% CI [1.04;2.21. Short sleep duration meaningfully contributed to the association between adult occupational position and CHD in men, with 13.4% mediation. Stroke did not exhibit a social patterning with any of the variables examined.

Conclusion

This study suggests that inadequate sleep accounts to a meaningful proportion of the association between adult occupational position and coronary heart disease, at least in men. With sleep increasingly being considered an important cardiovascular risk factor in its own terms, our study additionally points to its potential role in social inequalities in cardiovascular disease.

Translational perspective

This study, including data on 111,205 participants from eight cohorts in four European countries, suggests that inadequate sleep accounts for a meaningful proportion of the socioeconomic gradient in coronary heart disease, at least in men. With inadequate sleep increasingly being considered an important cardiovascular risk factor in its own terms, our study additionally points to its potential role in social inequalities in cardiovascular disease, and should encourage health professionals to consider these factors as major contributors to the pathophysiology of coronary heart disease.

Introduction

Individuals experiencing adverse socioeconomic circumstances across the life-course are disproportionately affected by cardiovascular disorders (CVD), including coronary heart disease and stroke [1, 2]. Social differences in cardiovascular disorders are partly explained by behavioral or psychosocial factors [3, 4]. However, a significant part of the socioeconomic gradient in cardiovascular disease remains unexplained [4].

Among the factors that may potentially link social disadvantage to CVD is inadequate sleep. First, individuals who experienced social adversity across the life-course report sleep-related problems more frequently than those with more advantaged experiences [5-7]. In particular, people working in shifts, living in deprived neighborhoods, or who have experienced adversity in childhood show an increased prevalence of sleep-related disorders [6, 8-12].

Second, inadequate sleep has been associated with an increased risk of cardiovascular disease [13-15]. Chronic sleep deprivation disrupts the function of several physiological systems including the dysregulation of key endocrine and metabolic processes, which may lead to an aberrant activation of the autonomous nervous system, and the impairment of immunity and inflammatory processes, altogether leading to an increased cardiovascular risk [13, 16, 17]. Excessively long sleep has also been associated with adverse cardiovascular health outcomes, although reverse causation processes whereby individuals sleep longer cannot be excluded [18-21]. To date, however, no large population-based study has assessed the contribution of sleep to the social gradient in CVD [8, 22].

In this study, we examine the associations between indicators of socioeconomic position (SEP) across the life-course and cardiovascular disorders, namely coronary heart disease (CHD) and stroke, by using cross-sectional data from eight cohort studies from four European

countries. Further, we assess to what extent the associations between life-course SEP and CVD are explained by sleep duration by applying the counterfactual mediation model.

Methods

Study population

This study is part of the Lifepath project [23] and uses cross-sectional data from eight cohorts: the French Constances (study period 2012-2016; N=65,843), E3N (2005-2006; N=51,841) and GAZEL (2014; N=10,203), the English Whitehall II (1997-1998; N=6,359) and ELSA (2012; N=5,083), the Swiss COLAUS (2009-2011; N=4,147) and SKIPOGH (2013-2016; N=979) and the Portuguese EPIPORTO (2005-2009; N=2,410) [11, 24-30]. While five cohorts included adults from the general population, E3N, GAZEL and Whitehall II were occupational cohorts and included women working in the French national education sector, employees of the French national gas and electricity company and British civil servants, respectively. All participants underwent a clinical examination and filled a questionnaire collecting data on demographic characteristics, health, medication, education, work, lifestyle and sleep characteristics.

Ethics statement

Each study was approved by relevant local or national ethics committees and all procedures performed in these studies were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants gave written informed consent. This study does not contain any studies with animals performed by any of the authors.

Measures

Life-course socioeconomic position

We used father's occupational position and last known adult occupational position as measures of SEP across the life-course. Father's occupational position is a common indicator of SEP in early life, whereas adult occupational position is the most used SEP indicator in adulthood [31]. Both variables capture multiple dimensions of SEP, including education, social prestige, wealth, and retirement benefits, and have been widely used in former studies exploring socioeconomic differences in health [32]. While father's occupational position was self-reported by study participants in all cohorts, adult occupational position was retrieved through work registries in GAZEL and Whitehall II studies, and self-reported in the six other cohorts (Supplementary Table 15). Both SEP indicators were coded according to the nine categories of the European Socio-economic Classification system (ESeC), which is a standard system for classifying professions in social epidemiology, and further grouped in three main categories: "High" (higher professionals/managers, lower professionals/managers, higher clerical), "Middle" (small employers and self-employed, farmers, lower supervisors and technicians) and "Low" (lower clerical, sales workers, skilled/unskilled workers) [33].

Cardiovascular disorders

Two cardiovascular disorders were considered as outcomes: coronary heart disease (CHD) and stroke. CHD was defined as reporting ischemic artery disease, angina pectoris, or myocardial infarction, whereas stroke was defined as reporting an ischemic or hemorrhagic stroke. The history of CVD events was based on self-report in GAZEL, ELSA, COLAUS, SKIPOGH and EPIPORTO studies, whereas an objective assessment of cardiovascular outcomes was available in Constances, E3N and Whitehall II cohorts, as these studies included thorough cardiological examinations at interview or had access to participant's medical records (Supplementary Table 15).

Sleep duration

Our study focused on sleep duration as this measure has previously been related to both SEP and CVD and was available in all eight cohorts [13, 34]. Sleep duration was self-reported in all eight cohorts as the average number of hours of sleep per night and subsequently categorized into recommended or normal sleep (6-8.5 h/night), short sleep (<6h/night) and long sleep (>8.5h/night). These thresholds were chosen from clinical practice which found that short sleep (<6h/night) was associated with an increased risk of CVD [14, 35], whereas long sleep (>8.5h/night) was related with preexistent conditions, such as depression [19, 36].

Other covariates

Potential confounders we considered included cohort, study period, health behaviors, and flexible working hours. Health behaviors were self-reported in all eight cohorts and included smoking, sedentary behavior and alcohol intake. Smoking status was categorized as current vs. former/never smoker, sedentary behavior was categorized as sedentary vs. non-sedentary based on the amount, frequency, and type of physical activity, whereas alcohol intake was categorized as hazardous intake (>3 daily alcohol units for men, >2 daily alcohol units for women) vs. non-hazardous intake. Flexible working hours were based on the ESeC classification of professions and were categorized as flexible (higher professionals and managers, lower professionals and managers; higher clerical, services and sales workers) and non-flexible (small employers and self-employed; farmers; lower supervisors; technicians; lower clerical, services and sales workers, skilled and unskilled workers).

Statistical analyses

We tested the association between adult or father's occupational position (main exposure variables) and sleep duration (outcome), using a multinomial logistic regression model adjusted for age, cohort, study period, health behaviors, and flexible working hours. To

account for the effect of adult occupational position in analyses using father's occupational position as the main exposure, we implemented an additional model that was further adjusted for adult occupational position [37]. We used the same set of covariates for the logistic model assessing the association between sleep duration (exposure) and CVD (outcome). We tested the associations between SEP indicators and cardiovascular disorders and the mediating effect of each level of sleep duration by applying the counterfactual mediation method, using the same sets of covariates. The counterfactual mediation method is based on two regression models (Annex 1): a first model predicting the outcome (CHD, stroke) based on the main exposure variable (SEP), the mediator (sleep duration), an interaction term between the main exposure and the mediator, and confounders, and a second regression model predicting the mediator based on the main exposure and confounders. The regression coefficients from the two models are subsequently used to compute counterfactual mediation estimates (Figure 1), namely the natural direct effects (NDE(odds ratio): effect of exposure on the outcome via pathways that do not involve the mediator), natural indirect effects (NIE(odds ratio): effect of exposure on the outcome operating through the mediator), marginal total effects (MTE(odds ratio)=NIE+NDE, total effect of the exposure on the outcome), and the proportion of the association between the exposure and the outcome which is mediated by the mediator (Proportion mediated-PM) [38]. Confidence intervals for MTE, NDE, NIE and PM parameters were computed through bootstrap procedure (random sample with replacement - 10,000 simulations). The main statistical analyses were conducted using Stata v.14 (Stata Corp, TX, USA). Statistical significances were set at p-value <0.05.

Individual cohort associations

To investigate for potential differences between individual cohorts, we repeated the associations between SEP and sleep duration, sleep duration and CVD, and the counterfactual

mediation models between SEP, sleep duration and CVD, cohort by cohort. We also performed a meta-analysis of the eight individual cohorts to examine which studies contributed the most to the pooled data associations, and to explore the inter-study heterogeneity by computing the I2 coefficient.

Additional sensitivity analyses

Cox regression models for time-to-event event longitudinal analyses

To examine whether the cross-sectional approach could have biased the main findings, we also conducted a series of longitudinal analyses using Cox regression models for the associations between SEP at baseline and CVD occurrence, and between sleep duration at baseline and CVD occurrence, using time-to-event data from Whitehall II study through waves 1 to 8 (w1 1985-1988, w2 1989-1990, w3 1991-1993, w4 1995-1996, w5 1997-1999, w6 2001, w7 2003-2004, w8 2006)[27]. We included 6805 individuals with complete data at waves 1-8, and tested the proportional hazard assumptions for Cox regression models by using log-log plots (not violated).

Multiple imputation for missing data for health behaviors

To test for bias that would result from missing values, we imputed missing data for health behaviors (confounding factors) using chained equations based on SEP, cardiovascular disorders and major confounders (Stata procedure "mi") [39].

Confounding by sleep quality indicators and other cardiometabolic disorders

We further explored potential confounding effects by four binary sleep quality indicators, namely "Difficulty falling asleep", "Difficulty waking up in the morning", "Waking up during the night", and "Waking up too early", by including them as covariables in counterfactual

mediation analyses between SEP indicators, sleep duration, and CVD (Annex 1). We also explored the potential confounding/contribution to the main associations by further adjusting for two major cardiometabolic disorders, namely type 2 diabetes (T2D), and obesity (Annex 2).

Comparison of studies using objective assessment vs. self-reported data

To investigate whether the methodology of data acquisition could have affected our findings, we compared the gradients for the associations between SEP and sleep duration, sleep duration and CVD, and the mediation by sleep duration to the SEP gradient in CVD, between cohorts that either used an objective assessment of the data for the main endpoints (Constances, E3N, Whitehall II) cohorts that were based on self-report (GAZEL, ELSA, COLAUS, SKIPOGH, EPIPORTO).

Education as the main SEP indicator

In addition to father's and adult occupational position, we also used education as the main exposure variable, in order to examine the association between education and sleep duration, and to assess the contribution of sleep duration to the educational gradient in CVD.

Extreme sleep duration thresholds

Finally, we repeated the associations between SEP and sleep duration, sleep duration and CVD, and the contribution of sleep duration to the SEP gradient in CVD using extreme sleep duration thresholds, namely 0h-5h for short sleep duration, and >10h for long sleep duration.

Results

From the initial 188,238 participants from the eight cohorts, 37,682 were excluded due to missing information on health behaviors, 3,691 for missing sleep duration, 17,328 for missing

adult occupational position, and 18,332 participants for missing father's occupational position, leaving a total of 111,205 participants to be included in the study. Excluded participants were more frequently women (73% vs. 67%) and had a lower adult occupational position than those included in the study (20% vs. 26% in the high occupation group).

Sample characteristics

We report the characteristics of the study population in **Table 1**. In the majority of the cohorts, low and middle father's occupational positions were the most prevalent, whereas the distribution of adult occupational position varied among studies and countries, with high and middle adult SEP groups being generally more prevalent in English cohorts, and low and middle adult SEP groups being more common in Southern European cohorts. The prevalence of short sleep ranged between 3% and 14% (6% for pooled data) and was higher in ELSA (14%) and lower in E3N and EPIPORTO (3% and 5%, respectively), while the prevalence of long sleep ranged between 9% and 27%, and was lower in Whitehall II, SKIPOGH and COLAUS (2%-5%), and higher in EPIPORTO (27%). The distribution of detrimental health behaviors varied substantially across the cohorts, and prevalence estimates ranged between 7% and 26% for current smoking, between 8% and 42% for hazardous alcohol intake, and between 6% and 81% for sedentary behavior. The prevalence of CHD ranged between 1% and 13%, with highest prevalence estimates being observed in Whitehall II and ELSA (13%), while the prevalence of stroke ranged between 1% and 5%, with highest prevalence being in ELSA.

Association between life-course SEP indicators and sleep duration

We show the association between life-course SEP indicators and sleep duration using pooled data in **Table 2**. We found a U-shaped association between father's occupational position and

sleep duration, with low SEP being more strongly associated with short sleep (A. Odds Ratio(OR)=1.18, 95% Confidence Interval(CI)[1.07;1.31], women: OR=1.31, 95% CI [1.20;1.44]), than long sleep (A. OR=1.01, 95% CI [0.92;1.11], women: OR=1.07, 95% CI [1.01;1.14]). The association between father's occupational position and sleep duration persisted after accounting for adult SEP. Larger effect size and stronger associations were observed for the association between adult occupational position and sleep duration, with stronger associations in men than in women. As for father's occupational position, however, we found stronger associations for short sleep (men: OR=2.22, 95% CI [1.85;2.66], women: OR=2.12, 95% CI [1.82;2.47]), than for long sleep (men: OR=1.88, 95% CI [1.59;2.23], women: OR=1.14, 95% CI [1.03;1.27]).

Association between sleep duration and cardiovascular disorders

The association between sleep duration and cardiovascular disorders is presented in **Table 3**. Short sleep was associated with an increased risk of CHD in both sexes (CHD-men: OR=1.65, 95% CI [1.41;1.92]; women: OR=1.59, 95% CI [1.28;1.97]), whereas it was associated with an increased risk of stroke in women but not in men (Stroke-men: OR=1.16, 95% CI [0.84;1.60]; women: OR=1.31, 95% CI [1.03;1.66]). We also observed a higher risk of stroke in participants with long sleep (men: OR=1.51, 95% CI [1.17;1.95]; women: OR=1.24, 95% CI [1.06;1.49]), while long sleep was also associated with an increased risk of CHD in women (OR=1.24, 95% CI [1.03;1.43]).

Association between life-course SEP indicators and CVD, and the contribution of sleep duration

In **Table 4**, we present the counterfactual mediation models for the associations between SEP indicators and cardiovascular disorders, mediated by short sleep duration. We observed an

inverse association between father's occupational position and CHD in both men and women (A. men: marginal total effect (MTE – OR scale)=1.19 95% CI [1.04;1.37], women: MTE (OR) = 1.25 95% CI [1.02;1.55]). Upon accounting for the effect of adult occupational position, the gradient between father's occupational position and CHD was marginally decreased (B. men: MTE (OR)=1.17 95% CI [1.02;1.35], women: MTE (OR) = 1.22 95% CI [0.99;1.51]). Sleep did not mediate the association between father's occupational position and stroke. We found a strong inverse association between adult occupational position and CHD risk in both sexes (C. men: MTE (OR)=1.45 95% CI [1.13;1.86], women: MTE (OR) = 1.52 95% CI [1.07;2.11]), with 13.4% mediation of this association by short sleep duration in men. We also evaluated the contribution of *long* sleep duration to the life-course socioeconomic gradient in cardiovascular disorders, but found no meaningful mediation **(Supplementary Table 1)**.

Individual cohort associations

We further examined the associations between SEP and sleep duration, sleep duration and cardiovascular disorders, and the mediating effect of short sleep duration to the association between SEP and cardiovascular disorders on each cohort separately **(Supplementary Tables 2-8)**. Overall, we found that low adult occupational position was associated with an increased risk of short and long sleep duration in the majority of cohorts (Constances, E3N, Whitehall II, ELSA, COLAUS, SKIPOGH, EPIPORTO), with generally stronger odds ratios for short sleep than long sleep, whereas there were fewer associations between father's occupational position and sleep duration, with stronger associations in the model unadjusted for adult occupational position. We also found associations between short sleep duration and an increased risk of CHD, with significant associations being observed in Constances, GAZEL, E3N and Whitehall II cohorts, whereas there were fewer associations between sleep duration

and stroke, in both unadjusted and adjusted models for adult occupational position. Furthermore, in most of the studies, results from mediation analyses were uninformative and yielded non-significant estimates for the mediation by short sleep duration due to low statistical power, the few exceptions being the inverse associations between father's occupational position and CHD in Constances and Whitehall II studies (**Supplementary Tables 6-7**), and a strong inverse association between adult occupational position and CHD in Whitehall II (**Supplementary Table 8**). Finally, we performed a meta-analysis using adult occupational position, sleep duration, and CHD, in order to examine which cohorts contributed the most to the pooled data associations (weights), and to examine the degree of heterogeneity across the cohorts (Supplementary Figure 1). We found a high inter-study heterogeneity for the SEP-sleep duration gradient, while there were more consistent gradients for the associations between sleep duration and CHD, the adult occupational gradient in CHD (MTE), and the mediating effect by sleep duration (NIE) across the cohorts. The observed heterogeneity for the SEP-sleep duration gradient may be explained by the different gradients found in GAZEL, SKIPOGH, and EPIPORTO studies when compared to the other cohorts. A possible explanation for these differences may be the lack of statistical power, as well as a weaker socioeconomic patterning of sleep duration in these studies.

Additional sensitivity analyses

Cox regression models for time-to-event event longitudinal analyses

As there is currently no methodology allowing to apply counterfactual mediation modelling to time-to-event longitudinal analysis, main analyses presented in this study were performed cross-sectionally. To assess whether this may have biased our findings for the main associations examined, the one between adult SEP and CVD and the one between sleep duration and CVD, we repeated the analysis using a longitudinal design in a cohort where

repeated data was available (Whitehall II). Using time-to-event analyses fitted through Cox regression models, we observed that low occupational position and short sleep (baseline, wave 1) were systematically associated with a higher risk of CHD events through waves 1 to 8 when compared to higher adult occupational position, and normal or long sleep duration. There were no clear gradients in women and for stroke, likely due to lack of statistical power and insufficient number of events (Supplementary Tables 9-10; Supplementary Figures 2-3).

Multiple imputation for missing data for health behaviors

We performed further sensitivity analyses by imputing missing values for confounders using chained equations, and by investigating the potential confounding effects of four sleep quality indicators in the cohorts where this information was available. We observed that there were no important differences between the associations using the complete case data from those using imputed data (**Supplementary Tables 11-12, Tables 2-3**).

Confounding by sleep quality indicators

We also found that sleep quality indicators could act as potential confounders of the association between life-course SEP, sleep duration, and CVD, as they were simultaneously associated with sleep duration and CVD in the counterfactual models (**Supplementary Tables 13-14**).

Comparison of studies using objective assessment vs. self-reported data

We further investigated whether the fact that several data were self-reported could have biased our results by comparing the associations between SEP and sleep duration, sleep duration and CHD, the association between SEP and CHD (MTE), and the mediation of this association by sleep duration between cohorts that used objective assessment of CHD and

those with self-reported data (**Supplementary Tables 16-18**). Results from cohorts that used objectively assessed data provided systematically stronger gradients than cohorts that were based on self-report, including meaningful mediation by short sleep duration (11.1%). However, we cannot conclude that these differences are exclusively attributed to the assessment method of CHD, as there were major regional differences between the two groups of cohorts.

Education as the main SEP indicator

We also investigated to what extent education was associated with sleep duration, and whether the educational gradient in CVD outcomes was mediated by short sleep duration (**Supplementary Tables 19-20**). We observed that low education was associated with an increased risk of short sleep duration and a higher risk for CHD, and that this association was significantly mediated by short sleep duration (9.2%). These associations and mediation were systematically weaker than those involving adult occupational position, and somewhat higher compared to associations using father's occupational position as main exposure.

Confounding/contribution by cardiometabolic disorders

Moreover, we also performed a series of additional analyses where associations between adult occupational position, sleep duration, and CHD were further adjusted for type 2 diabetes and obesity (**Supplementary Tables 21-23**). We observed that the associations between adult SEP and short sleep, and between short sleep and CHD were attenuated upon adjustment for type 2 diabetes (T2D) and obesity, whereas the association between SEP and CHD and the contribution of short sleep duration to this association were no longer significant.

Extreme sleep duration thresholds

Finally, we also examined the associations between adult SEP, sleep duration, and CHD, using more extreme thresholds for sleep duration; 0h-5h for short sleep duration, and >10h for long sleep duration (**Supplementary Tables 24-26**). We generally found stronger gradients for the association between adult SEP and extreme sleep duration, and for extreme sleep duration and CHD, in particular for the 0h-5h sleep duration category. These findings indicate that extreme sleep patterns are more prevalent among socially disadvantaged individuals, and that they have stronger effects on cardiovascular outcomes. Furthermore, we also observed that there was a somewhat weaker mediation by extreme short sleep duration (0h-5h) when compared to the former threshold (0h-6h), which was due to a weaker indirect effect (NIE).

Discussion

In this study, we found that both father's and adult occupational position were associated with abnormal sleep duration patterns, with stronger associations for adult than for early life SEP, and for short sleep than for long sleep. Furthermore, abnormal sleep duration was associated with an increased risk of cardiovascular disorders, with stronger associations for short sleep than for long sleep. Finally, we observed that there were inverse associations between both life-course SEP indicators and CHD, and that the association between adult occupational position and CHD was partly explained by short sleep duration, at least in men.

Our results on life-course socioeconomic gradient in short sleep duration tend to be in line with previous studies [6, 12, 34]. Former research has reported that adverse socioeconomic circumstances in childhood affect sleep health in adulthood through a latent effect, and that this association may be related to the fact that stressful childhood experiences lead to disrupted emotion regulation in adulthood, which in turn has a negative impact on adult sleep [12, 40]. The adult occupational gradient in sleep duration may be related to the fact that individuals with lower grade occupations often have to combine several jobs, work in shifts,

and live in noisy environments, thus experiencing greater levels of stress, altogether leading to sleep deprivation [5, 11, 22]. The stronger association between adult occupational position and short sleep duration when compared with father's occupational position and education may be related to the fact that adult occupational position directly acts on proximal exposures which affect sleep, such as poor housing, work stress, and recent psychosocial exposures, whereas father's occupational position and education likely act through more indirect effects that have occurred in early life [7, 40, 41]. Interestingly, we also observed that individuals with low father's and adult occupational position were more likely to have excessively long sleep duration, when compared to high SEP individuals. However, while short sleep duration is more probably the consequence of adverse socioeconomic circumstances, later leading to adverse health outcomes, long sleep duration more probably results from preexisting conditions, such as depression, that affect socially disadvantaged individuals more [18-21, 35].

Our study also confirms the relationship between short sleep duration and an increased risk of CHD and stroke [13]. Mechanistic studies suggest that chronic sleep deprivation may result in hypertension, elevated inflammation, and atherosclerosis through an aberrant activation of the sympathetic nervous system, as well as to an increased risk of type 2 diabetes (T2D) and obesity, altogether leading to cardiovascular events [13, 15, 42]. In a series of sensitivity analyses additionally adjusted for T2D and obesity, we observed that the association between adult SEP and CHD, and the contribution of sleep duration were no longer significant, which may be attributed to potential confounding or even mediation, whereby T2D and obesity could constitute an additional intermediate step between chronic sleep deprivation, and the eventual occurrence of CHD or stroke. The potential role of inappropriate nutrition as an

additional step in this chain of causation could not be investigated in our study and shall be the subject of additional research.

We also found that long sleep duration is associated with an increased CVD risk, but to a lesser extent than short sleep, which is line with previous studies reporting that an excessively long sleep duration is also associated with adverse health outcomes, including CVD [21]. Nevertheless, the underlying mechanisms linking sleep duration and CVD are not the same for short and long sleep duration, and long sleep duration is often mentioned as a consequence of preexisting illnesses rather than a cause [18-21]. While there is no clear evidence that sleeping more than eight hours per night could lead to adverse health outcomes in healthy individuals, former research has often reported that major depressive disorder is a strong predictor of excessive sleeping, suggesting that depression may confound the associations between long sleep and adverse health-related outcomes[18].

Our study found that there was an inverse association between adult occupational position and CHD in both men and women, which is in line with previous research [43]. We also observed that short sleep duration significantly contributed to the adult occupational gradient in CHD in men, but not in women. The absence of mediation by short sleep duration in women may be related to the fact that there was a weaker adult occupational gradient in short sleep duration in women than in men. Overall, these gender-related differences may be explained by additional sociodemographic and socioeconomic factors, such as the fact that low SEP women often have to combine the physical and psychosocial strain of manual, less paid jobs to that of numerous household responsibilities and stress, which eventually negatively affects their sleep and its health-restoring effects when compared to men [11]. Furthermore, we found an inverse association between father's occupational position and CHD, which was only marginally decreased upon accounting for adult occupational position. These findings indicate

that father's occupational position likely affects CHD through latent mechanisms, whereby adverse socioeconomic circumstances in early life have left permanent biological imprints that translate into higher CHD risk in later life [37, 44]. Finally, we also observed that there were no associations between both life-course SEP indicators and stroke, which may be related to a differential socioeconomic patterning, and different pathophysiology and risk factors for these two cardiovascular disorders [45, 46] . Another explanation may be related to a lack of statistical power, as the occurrence of stroke was much lower than the occurrence of CHD events throughout the included cohorts.

Strengths and limitations

Our study has several strengths. First, to our knowledge this is the first study to investigate the contribution of sleep duration to the association between life-course socioeconomic position and cardiovascular disorders. Second, we used data from eight cohorts conducted in four European countries, involving more than 111,000 participants. Our study also has some limitations to acknowledge. First, the demographic, epidemiological and methodological differences between the eight cohorts represent a vast challenge in terms of data harmonization, and may result in important heterogeneity, particularly concerning the occurrence and assessment of cardiovascular outcomes. While the difference in CHD prevalence between the Northern (Whitehall II, ELSA) and the Southern European cohorts (Constances, E3N, GAZEL, SKIPOGH, COLAUS) may be attributed to the well-established North-South gradient in CHD prevalence in Europe [47], potential bias resulting from a differential reporting of cardiovascular outcomes cannot be excluded. In particular, the absence of objectively assessed health-related outcomes and the lack of access to medical records may result in important self-report and recall biases, eventually yielding differential SEP-CVD and sleep duration-CVD gradients across included studies [48, 49]. These types of

systematic errors represent an important issue in epidemiological studies, especially given the fact that factors such as education and other SEP variables were found to influence recall bias in retrospective cohorts [48]. Furthermore, another limitation related to procurement methodology is the systematic difference observed between self-reported and objectively measured sleep duration, which could not be accounted for in the present analyses [50]. Additional issues may be related to the statistical methodology applied in this study. In particular, cross-sectional analyses do not allow determining the causal direction of associations, which can be a particular issue for analyses involving sleep disturbances and health-related outcomes, as the relation between these two factors is not exclusively unidirectional. However, we managed to address this issue by performing a series of longitudinal analyses in Whitehall II study. Furthermore, apart from the contribution of sleep duration, we must acknowledge the role of other potential confounders or mediators of the socioeconomic gradient in cardiovascular disorders, including hypertension, hyperlipidemia, life-related factors, working hours, psychosocial exposures, and environmental factors, whose contribution was not examined in this multi-cohort study. Finally, the lack of information on objectively measured sleep disorders (i.e. sleep-disordered breathing) as well as sleep quality indicators in the majority of cohorts may be another limiting factor in this study, as sleep apnea and sleep quality have been found to be associated with CVD risk as well as sleep duration, and could potentially confound the causal pathways involving SEP, sleep duration, and cardiovascular disorders [51-53].

Conclusion

In summary, this large pan-European analysis suggests that short sleep duration is a potential mechanism underlying the association between adult occupational position and CHD. Additional longitudinal analyses shall be conducted to further investigate the causal

relationship between SEP, sleep duration and CVD. Finally, the role of other sleep features, in particular sleep quality, shall further be investigated as potential confounders of the associations between SEP, sleep duration, and CVD.

Author's contributions

SS, DP, CC and MCH designed the study. JHR, MK-I, PVi, MK, MG, FR, AD'E, MB, PVo, HB, SF, MG, MZ, AS, CD, RH, and SS actively contributed to data acquisition and harmonization. DP, SN, SS, CC, MCH analyzed the data. DP, SS, CC, MCH, JHR, CDM, MK-I, PVi, MK, SN, MG, FR, AD'E, MB, PVo, HB, SF, MG, MZ, AS, CD, RH critically revised the manuscript.

LIFEPATH Consortium

Harri Alenius, Mauricio Avendano, Henrique Barros, Murielle Bochud, Cristian Carmeli, Luca Carra, Raphaele Castagne, Marc Chadeau-Hyam, Francoise Clavel-Chapelon, Giuseppe Costa, Emilie Courtin, Carlos de Mestral Vargas, Cyrille Delpierre, Angelo d'Errico, Pierre-Antoine Dugue, Paul Elliott, Silvia Fraga, Valerie Gares, Graham Giles, Marcel Goldberg, Dario Greco, Allison Hodge, Michelle Kelly Irving, Piia Karisola, Maryam Karimi, Mika Kivimaki, Vittorio Krogh, Jessica Laine, Thierry Lang, Richard Layte, Benoit Lepage, Johan Mackenbach, Michael Marmot, Cathal McCrory, Roger Milne, Peter Muennig, Wilma Nusselder, Salvatore Panico, Dusan Petrovic, Silvia Polidoro, Martin Preisig, Olli Raitakari, Ana Isabel Ribeiro, Fulvio Ricceri, Oliver Robinson, Jose Rubio Valverde, Carlotta Sacerdote, Roberto Satolli, Gianluca Severi, Martin J Shipley, Terrence Simmons, Silvia Stringhini, Lanre Thomas, Rosario Tumino, Paolo Vineis, Peter Vollenweider, and Marie Zins.

Funding

This work was supported by the Lifepath project, which is funded by the European commission (Horizon 2020 grant 633666), the Swiss state secretariat for education, research and innovation – SERI, the Swiss National Science Foundation, the Medical Research Council and the Portuguese Foundation for Science.
The CONSTANCES Cohort is supported by the Caisse Nationale d'Assurance Maladie des travailleurs salariés-CNAMTS, and is funded by the Institut de Recherche en Santé Publique/Institut Thématique Santé Publique, and the following sponsors: Ministère de la santé et des sports, Ministère délégué à la recherche, Institut national de la santé et de la recherche médicale, Institut national du cancer et Caisse nationale de solidarité pour l'autonomie [24]. The GAZEL cohort was partly supported by the Agence Nationale De La Recherche (Grant ANR-08-BLAN-0028-01) and the Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (Grant AFSSET-EST08-35). The GAZEL Cohort Study was partly funded by Electricité de France-Gaz de France and the TGIR Cohortes Santé 2008 Program [26]. The E3N study has been conducted with financial support from the Mutuelle Générale de l'Education Nationale (MGEN); French League against Cancer (LNCC); Gustave Roussy Institute (IGR); French Institute of Health and Medical Research (Inserm); and the European Union through participation in EPIC. Additional funds have also been obtained from research grants, mostly from French institutions such as the Institut National du Cancer, Fondation de France, Fondation ARC pour la Recherche sur le Cancer, Ligue nationale contre le Cancer, Agence nationale de Sécurité du Médicament and Agence Nationale de la Recherche, and from the European Union [25]. The Whitehall II study has been supported by grants from the MRC; the Economic and Social Research Council; the British Heart Foundation; the Health and Safety Executive; the Department of Health; the National Heart, Lung, and Blood Institute (Grant HL36310), US, NIH; the National Institute on Aging (Grant AG13196), US, NIH; the Agency for Health Care Policy Research (HS06516); and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health. In addition, there are some grant organizations that have funded specific parts of the study, e.g. the ESRC; the Health Development Agency; Volvo; the European Union; The New England Medical Centre, Division of Health Improvement; the Institute for Work and Health, Toronto [27]. The ELSA study was funded by the UK National Institute on Aging, Departments of Education and Skills,

Environment, Food and Rural Affairs, Health, Trade and Industry, Work and Pensions, Her Majesty's Treasury, Inland Revenue, the Office of the Deputy Prime Minister and Office for National Statistics [28]. The SKIPOGH study is supported by a grant from the Swiss national science foundation (Grant FN 33CM30-124087) [29]. The CoLaus|PsyCoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science foundation (Grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401) [11]. The EPIPorto study was funded by Fundação para a Ciência e a Tecnologia, POCTI/ESP/42361/2001, POCI/SAU-ESP/61160/ 2004, and PTDC/SAU-ESA/108315/2008 [30]. **The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; and preparation, review or approval of the manuscript.**

Acknowledgments

The authors would like to express their gratitude to Dr. Saman Khalatbari Soltani (IUMSP) for critically revising and helping improve this manuscript. The authors would also like to thank all the collaborators of the Lifepath project (http://www.lifepathproject.eu/), as well as all the cohort members and participants who contributed to this pan-European project.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Adler, N.E., et al., *Socioeconomic inequalities in health: no easy solution.* Jama, 1993. **269**(24): p. 3140-3145.
2. Smith, G.D. and C. Hart, *Life-course socioeconomic and behavioral influences on cardiovascular disease mortality: the collaborative study.* American Journal of Public Health, 2002. **92**(8): p. 1295-1298.
3. Matthews, K.A., L.C. Gallo, and S.E. Taylor, *Are psychosocial factors mediators of socioeconomic position and health connections?* Annals of the New York academy of sciences, 2010. **1186**(1): p. 146-173.
4. Petrovic, D., et al., *The contribution of health behaviors to socioeconomic inequalities in health: A systematic review.* Preventive medicine, 2018.
5. Anders, M.P., et al., *Association between socioeconomic factors and sleep quality in an urban population-based sample in Germany.* The European Journal of Public Health, 2013. **24**(6): p. 968-973.
6. Jarrin, D.C., et al., *Objective and subjective socioeconomic gradients exist for sleep quality, sleep latency, sleep duration, weekend oversleep, and daytime sleepiness in adults.* Behavioral sleep medicine, 2013. **11**(2): p. 144-158.
7. Stamatakis, K.A., G.A. Kaplan, and R.E. Roberts, *Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 years of follow-up.* Annals of epidemiology, 2007. **17**(12): p. 948-955.
8. Van Cauter, E. and K. Spiegel, *Sleep as a mediator of the relationship between socioeconomic position and health: a hypothesis.* Annals of the New York Academy of Sciences, 1999. **896**(1): p. 254-261.
9. Hill, T.D., A.M. Burdette, and L. Hale, *Neighborhood disorder, sleep quality, and psychological distress: testing a model of structural amplification.* Health & place, 2009. **15**(4): p. 1006-1013.
10. Grandner, M.A., et al., *Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints.* Sleep medicine, 2010. **11**(5): p. 470-478.
11. Stringhini, S., et al., *Association of socioeconomic position with sleep disturbances in the Swiss population-based CoLaus study.* Sleep medicine, 2015. **16**(4): p. 469-476.
12. Tomfohr, L.M., S. Ancoli-Israel, and J.E. Dimsdale, *Childhood socioeconomic position and race are associated with adult sleep.* Behav Sleep Med, 2010. **8**(4): p. 219-30.
13. Mullington, J.M., et al., *Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation.* Progress in cardiovascular diseases, 2009. **51**(4): p. 294-302.
14. Ayas, N.T., et al., *A prospective study of sleep duration and coronary heart disease in women.* Archives of internal medicine, 2003. **163**(2): p. 205-209.
15. Cappuccio, F.P. and M.A. Miller, *Sleep and Cardio-Metabolic Disease.* Current Cardiology Reports, 2017. **19**(11): p. 110.
16. Motivala, S.J. and M.R. Irwin, *Sleep and immunity: cytokine pathways linking sleep and health outcomes.* Current Directions in Psychological Science, 2007. **16**(1): p. 21-25.
17. Born, J., S. Muth, and H. Fehm, *The significance of sleep onset and slow wave sleep for nocturnal release of growth hormone (GH) and cortisol.* Psychoneuroendocrinology, 1988. **13**(3): p. 233-243.
18. Patel, S.R., et al., *Correlates of long sleep duration.* Sleep, 2006. **29**(7): p. 881.
19. Knutson, K.L. and F.W. Turek, *The U-shaped association between sleep and health: the 2 peaks do not mean the same thing.* Sleep, 2006. **29**(7): p. 878-879.
20. Stranges, S., et al., *Correlates of short and long sleep duration: a cross-cultural comparison between the United Kingdom and the United States: the Whitehall II Study and the Western New York Health Study.* American journal of epidemiology, 2008. **168**(12): p. 1353-1364.
21. Buxton, O.M. and E. Marcelli, *Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States.* Social science & medicine, 2010. **71**(5): p. 1027-1036.

22. Sekine, M., et al., *Explaining social inequalities in health by sleep: the Japanese civil servants study.* Journal of Public Health, 2006. **28**(1): p. 63-70.
23. Stringhini, S., et al., *Socioeconomic position and the 25× 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1· 7 million men and women.* The Lancet, 2017. **389**(10075): p. 1229-1237.
24. Zins, M., et al., *The CONSTANCES cohort: an open epidemiological laboratory.* BMC public health, 2010. **10**(1): p. 479.
25. Clavel-Chapelon, F. and E.N.S. Group, *Cohort profile: the French E3N cohort study.* International journal of epidemiology, 2014. **44**(3): p. 801-809.
26. Goldberg, M., A. Leclerc, and M. Zins, *Cohort profile update: the GAZEL cohort study.* International journal of epidemiology, 2014. **44**(1): p. 77-77g.
27. Marmot, M. and E. Brunner, *Cohort profile: the Whitehall II study.* International journal of epidemiology, 2005. **34**(2): p. 251-256.
28. Steptoe, A., et al., *Cohort profile: the English longitudinal study of ageing.* International journal of epidemiology, 2012. **42**(6): p. 1640-1648.
29. Petrovic, D., et al., *Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study.* Psychoneuroendocrinology, 2016. **67**: p. 76-85.
30. Fraga, S., et al., *Association of socioeconomic position with inflammatory markers: A two cohort comparison.* Preventive medicine, 2015. **71**: p. 12-19.
31. Galobardes, B., et al., *Indicators of socioeconomic position (part 1).* Journal of Epidemiology & Community Health, 2006. **60**(1): p. 7-12.
32. Stringhini, S., et al., *Association of lifecourse socioeconomic position with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study.* PLoS medicine, 2013. **10**(7): p. e1001479.
33. d'Errico, A., et al., *Socioeconomic indicators in epidemiologic research: A practical example from the LIFEPATH study.* PloS one, 2017. **12**(5): p. e0178071.
34. Ertel, K.A., L.F. Berkman, and O.M. Buxton, *Socioeconomic position, occupational characteristics, and sleep duration in African/Caribbean immigrants and US White health care workers.* Sleep, 2011. **34**(4): p. 509.
35. Steptoe, A., V. Peacey, and J. Wardle, *Sleep duration and health in young adults.* Archives of internal medicine, 2006. **166**(16): p. 1689-1692.
36. Patel, S.R., et al., *A prospective study of sleep duration and mortality risk in women.* SLEEP-NEW YORK THEN WESTCHESTER-, 2004. **27**(3): p. 440-444.
37. Marmot, M., et al., *Relative contribution of early life and adult socioeconomic factors to adult morbidity in the Whitehall II study.* Journal of Epidemiology & Community Health, 2001. **55**(5): p. 301-307.
38. Valeri, L. and T.J. VanderWeele, *Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros.* Psychological methods, 2013. **18**(2): p. 137.
39. Azur, M.J., et al., *Multiple imputation by chained equations: what is it and how does it work?* International journal of methods in psychiatric research, 2011. **20**(1): p. 40-49.
40. Gregory, A.M., et al., *Family Conflict in Childhood: A Predictor of Later Insomnia.* Sleep, 2006. **29**(8): p. 1063-1067.
41. Marmot, M. and R. Wilkinson, *Social Determinants of Health*. 2005: OUP Oxford.
42. Kato, M., et al., *Effects of sleep deprivation on neural circulatory control.* Hypertension, 2000. **35**(5): p. 1173-1175.
43. Stringhini, S., et al., *Health behaviours, socioeconomic position, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts.* PLoS medicine, 2011. **8**(2): p. e1000419.
44. Kuh, D., et al., *Life course epidemiology.* Journal of Epidemiology & Community Health, 2003. **57**(10): p. 778-783.
45. Salonen, J.T., *Socioeconomic position and risk of cancer, cerebral stroke, and death due to coronary heart disease and any disease: a longitudinal study in eastern Finland.* Journal of Epidemiology & Community Health, 1982. **36**(4): p. 294-297.

46. Rogot, E. and Z. Hrubec, *Trends in mortality from coronary heart disease and stroke among US veterans; 1954–1979.* Journal of clinical epidemiology, 1989. **42**(3): p. 245-256.
47. Müller-Nordhorn, J., et al., *An update on regional variation in cardiovascular mortality within Europe.* European heart journal, 2008. **29**(10): p. 1316-1326.
48. Coughlin, S.S., *Recall bias in epidemiologic studies.* Journal of clinical epidemiology, 1990. **43**(1): p. 87-91.
49. Kuper, H. and M. Marmot, *Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study.* Journal of Epidemiology & Community Health, 2003. **57**(2): p. 147-153.
50. Lauderdale, D.S., et al., *Self-reported and measured sleep duration: how similar are they?* Epidemiology (Cambridge, Mass.), 2008. **19**(6): p. 838-845.
51. Gami, A.S., et al., *Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation.* Journal of the American College of Cardiology, 2007. **49**(5): p. 565-571.
52. Hoevenaar-Blom, M.P., et al., *Sleep Duration and Sleep Quality in Relation to 12-Year Cardiovascular Disease Incidence: The MORGEN Study.* Sleep, 2011. **34**(11): p. 1487-1492.
53. Peker, Y.k., et al., *Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up.* American journal of respiratory and critical care medicine, 2002. **166**(2): p. 159-165.

Table 1: General characteristics of included participants by cohort

	Constances	GAZEL	E3N	Whitehall II	ELSA	COLAUS	SKIPOGH	EPIPORTO	Pooled data
	N=50,463	N=8,760	N=39,258	N=4,356	N=3,838	N=2,228	N=854	N=1,448	N=111,205
% Women	26437 (52%)	2059 (24%)	39258 (100%)	1239 (28%)	2144 (56%)	1149 (52%)	432 (51%)	864 (60%)	73582 (66%)
Age (mean±SD, y)	48.4 (±13)	68.9 (±3.4)	64 (±6.3)	55.7 (±6)	72 (±8.7)	53 (±8)	50.3 (±16.2)	52 (±13.3)	56.8 (±13.1)
Father's occupationnal position (N, %)									
High	10933 (22%)	3251 (37%)	6303 (16%)	426 (10%)	396 (10%)	718 (32%)	215 (25%)	195 (13%)	22437 (20%)
Middle	20504 (41%)	1930 (22%)	16805 (43%)	1335 (31%)	1476 (38%)	848 (38%)	406 (48%)	306 (21%)	43610 (39%)
Low	19026 (38%)	3579 (41%)	16150 (41%)	2595 (60%)	1966 (51%)	662 (30%)	233 (27%)	947 (65%)	45158 (41%)
Adult occupational position (N, %)									
High	17041 (34%)	2527 (29%)	5041 (13%)	2412 (55%)	1118 (29%)	352 (16%)	187 (22%)	310 (21%)	28988 (26%)
Middle	16402 (33%)	4649 (53%)	28411 (72%)	1350 (31%)	1679 (44%)	818 (37%)	293 (34%)	313 (22%)	53915 (48%)
Low	17020 (34%)	1584 (18%)	5806 (15%)	594 (14%)	1041 (27%)	1058 (47%)	374 (44%)	825 (57%)	28302 (25%)
Flexible working hours (N, %)	17041 (34%)	2527 (29%)	5041 (13%)	3762 (86%)	1118 (29%)	352 (16%)	185 (22%)	310 (21%)	30336 (27%)
Sleep duration (mean±SD, h/n)	7.2 (±1.2)	7.3 (±1.1)	7.6 (±1.1)	6.7 (±1)	6.9 (±1.3)	6.9 (±1)	6.9 (±1.1)	7.8 (±1.5)	7.3 (±1.2)
Sleep duration (N, %)									
Normal sleep (6h-8.5h/n)	40382 (80%)	6676 (76%)	31532 (80%)	3960 (91%)	2962 (77%)	1953 (88%)	728 (85%)	996 (69%)	89189 (80%)
Long sleep (>8.5h/n)	5934 (12%)	1376 (16%)	6670 (17%)	66 (2%)	325 (8%)	80 (4%)	42 (5%)	385 (27%)	14878 (13%)
Short sleep (<6h/n)	4147 (8%)	708 (8%)	1056 (3%)	330 (8%)	551 (14%)	195 (9%)	84 (10%)	67 (5%)	7138 (6%)
Health-related behaviors (N, %)									
Current smoking	9696 (19%)	635 (7%)	2639 (7%)	452 (10%)	354 (9%)	496 (22%)	224 (26%)	327 (23%)	14823 (13%)
Hazardous alcohol consumption [a]	5847 (12%)	2468 (28%)	16601 (42%)	1731 (40%)	1057 (28%)	401 (18%)	72 (8%)	475 (33%)	28652 (26%)
Sedentary behavior	11689 (23%)	2884 (33%)	7874 (20%)	259 (6%)	1280 (33%)	611 (27%)	337 (39%)	1169 (81%)	26103 (23%)
Diabetes (N, %)	1683 (3%)	1155 (13%)	***	204 (5%)	303 (12%)	176 (8%)	46 (5%)	165 (11%)	3732 (5%)
Obesity (N, %)	5676 (11%)	1177 (14%)	2660 (7%)	596 (18%)	945 (29%)	297 (13%)	123 (14%)	312 (22%)	11786 (11%)
Cardiovascular disorders									
CHD (N, %)	660 (1%)	518 (6%)	460 (1%)	574 (13%)	445 (13%)	93 (4%)	21 (2%)	92 (6%)	2863 (3%)
Stroke (N, %)	400 (1%)	99 (1%)	878 (2%)	18 (0%)	190 (5%)	24 (1%)	10 (1%)	36 (2%)	1655 (2%)

CHD, coronary heart disease; h/n, hours per night

[a] Hazardous alcohol consumption was defined as having >3 alcoholic drinks per day for men and >2 alcoholic drinks per day in women , *** This outcome was not assessed in the E3N cohort

Table 2: Association between SEP indicators and sleep duration based on pooled cohort data

Men		**OR (95 %CI)**	***P*-value**	**N**
A. Father's occupational position (unadj. adult occ.)	Short sleep (0h-6h)	1.18 [1.07;1.31]	0.002	37623
(High: 7.15h; Mid: 7.13h; Low: 7.07h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.01 [0.92;1.11]	0.805	
B. Father's occupational position (adj. adult occ.)	Short sleep (0h-6h)	1.12 [1.01;1.24]	0.036	37623
(High: 7.15h; Mid: 7.13h; Low: 7.07h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	0.97 [0.89;1.07]	0.560	
C. Adult occupational position	Short sleep (0h-6h)	2.22 [1.85;2.66]	<0.001	37623
(High: 7.11h; Mid: 7.12h; Low: 7.09h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.88 [1.59;2.23]	<0.001	
Women				
A. Father's occupational position (unadj. adult occ.)	Short sleep (0h-6h)	1.31 [1.20;1.44]	<0.001	73582
(High: 7.37h; Mid: 7.41h; Low: 7.37h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.07 [1.01;1.14]	0.014	
B. Father's occupational position (adj. adult occ.)	Short sleep (0h-6h)	1.24 [1.13;1.36]	<0.001	73582
(High: 7.37h; Mid: 7.41h; Low: 7.37h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.07 [1.01;1.13]	0.028	
C. Adult occupational position	Short sleep (0h-6h)	2.12 [1.82;2.47]	<0.001	73582
(High: 7.33h; Mid: 7.46h; Low: 7.27h) [d]	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.14 [1.03;1.27]	0.014	

OR, odds ratio; CI, confidence interval

A. Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

B. Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors

C. Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

[d] Average sleep duration per SEP categories

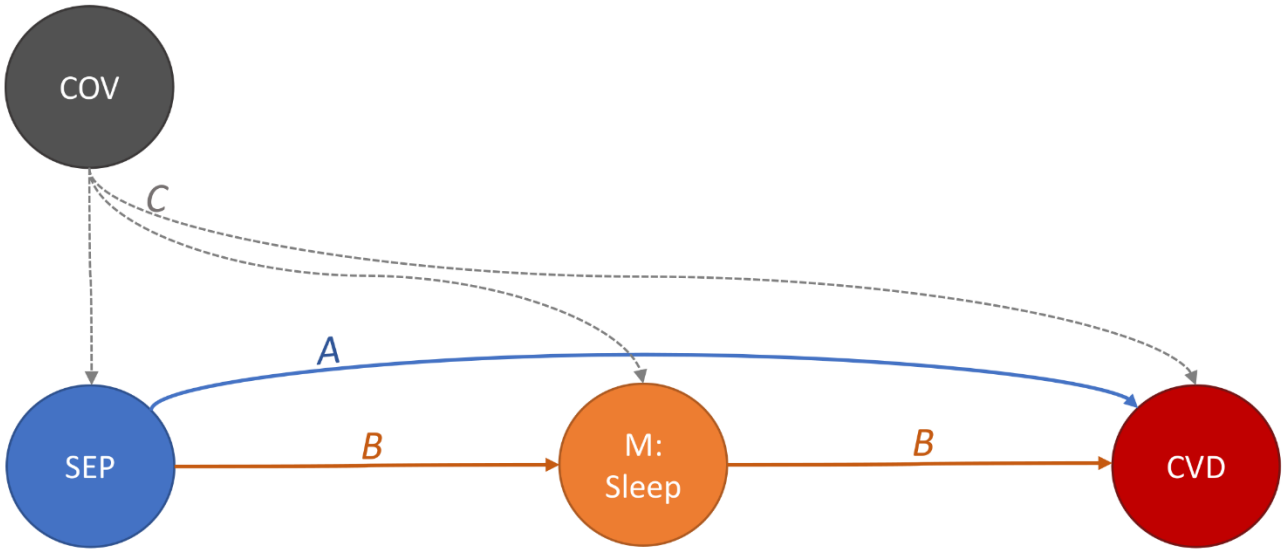
Table 3: Association between sleep duration and cardiovascular disorders based on pooled cohort data

			OR (95% CI) [a]	P-value	N
Men	Short sleep (0h-6h)	CHD	1.65 [1.41;1.92]	<0.001	36987
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.02 [0.87;1.19]	0.825	
	Short sleep (0h-6h)	Stroke	1.16 [0.84;1.60]	0.381	36759
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.51 [1.17;1.95]	0.001	
Women	Short sleep (0h-6h)	CHD	1.59 [1.28;1.97]	<0.001	72863
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.24 [1.03;1.49]	0.024	
	Short sleep (0h-6h)	Stroke	1.31 [1.03;1.66]	0.028	72819
	Normal sleep (6h-8.5h) (ref. predictor)		1.00		
	Long sleep (>8.5h)		1.24 [1.06;1.43]	0.005	

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

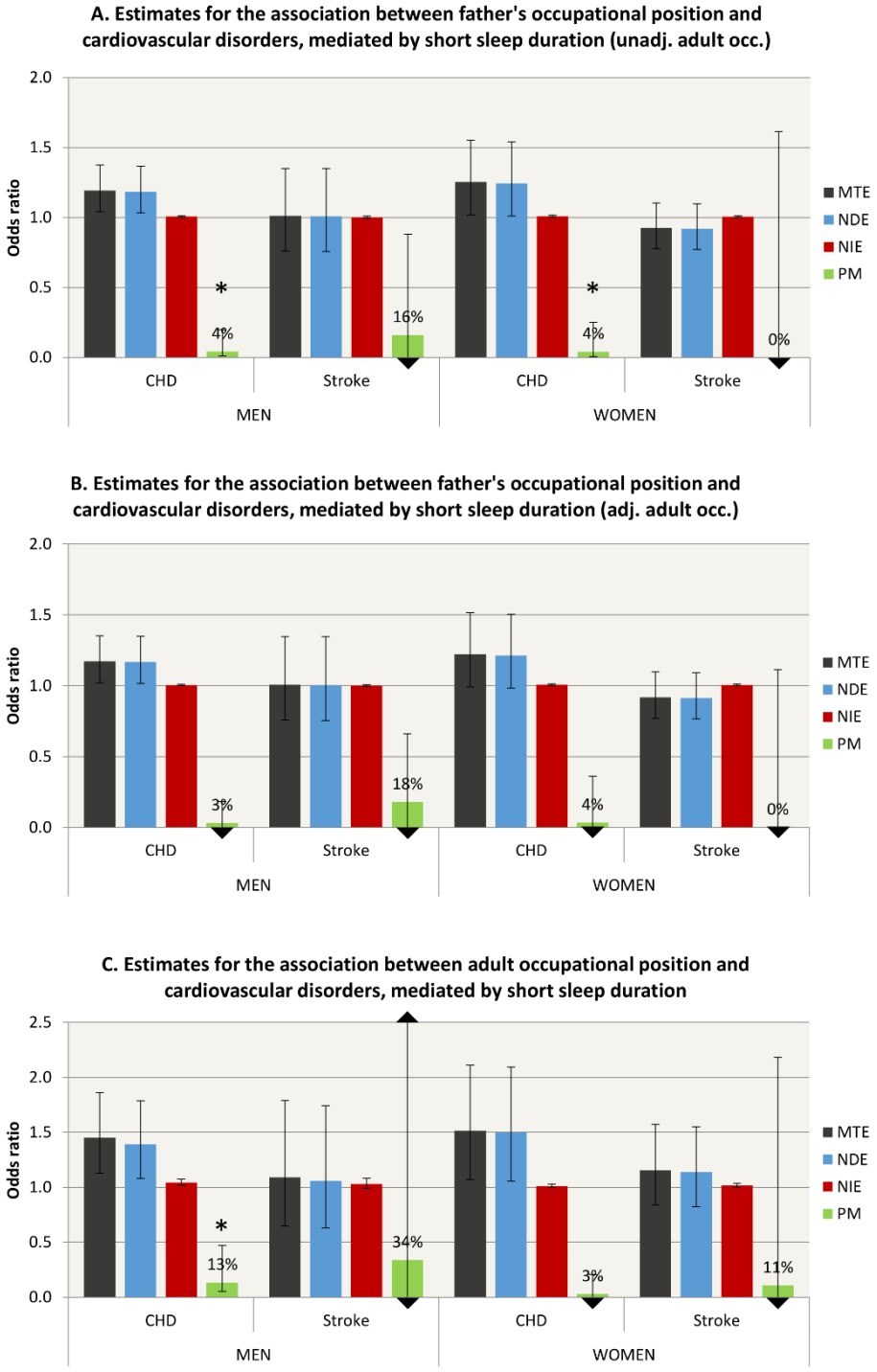
[a] Logistic regression for the association between three category sleep duration (categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and cardiovascular disorders (outcome), adjusted for age, cohort , study period, flexible working hours, and health behaviors

Figure 1: Directed acyclic graphs representing the counterfactual mediation model for the association between SEP indicators and cardiovascular outcomes, mediated by sleep duration



COV: Covariates (age, cohort, study period, health behaviors, flexible working hours); SEP: (Adult/Father's occupational position); M: mediator – sleep duration; CVD (cardiovascular disorders)
A: NDE, Natural direct effect: Effect of the predictor (SEP) on the main outcome (CVD), through pathways which do not involve the mediator (sleep duration)
B: NIE: Natural indirect effect: Effect of the predictor (SEP) on the main outcome (CVD), through pathways which involve the mediator (sleep duration)
C: Confounding effects by covariates
MTE: Marginal total effect of the predictor (SEP) on the main outcome (CVD): NDE + NIE (not represented)
This figure was realized with MS Office-Excel.

Figure 2: Counterfactual mediation estimates for the association between SEP indicators and cardiovascular disorders, mediated by short sleep duration (<6h/n), using pooled cohort data



CHD, coronary heart disease
A. Association between father's occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors
B. Association between father's occupational position and CVD, adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors
C. Association between adult occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors
Sample size (A, B, C): Men: N=36'987 CHD, N=36'759 stroke ; Women: N=72'863 CHD, N=72'819 stroke
MTE: Marginal total effect (OR95% CI); NDE: Natural direct effect (OR 95% CI); NIE: Natural indirect effect (OR 95% CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by short sleep duration (*****, significant mediation; Lower ▼ and upper ▲ arrow indicate that CIs extend beyond the limits of the graph)
This figure was realized with MSOffice-Excel.

Supplementary Table 1: Counterfactual mediation estimates for the association between SEP indicators and cardiovascular disorders, mediated by long sleep duration (>8.5h/n), using pooled cohort data

		MTE-OR (95%CI)	NDE-OR (95%CI)	NIE-OR (95%CI)	PM (95%CI)	N
A. Father's occupational position (unadj. adult occ.)						
Men	CHD	**1.18 [1.03;1.37]**	**1.18 [1.03;1.37]**	1.00 [0.99;1.01]	0.0 [-1.1;0.9]	36987
	Stroke	1.01 [0.77;1.34]	1.01 [0.77;1.33]	1.00 [0.99;1.01]	7.2 [-19.4;18.6]	36759
Women	CHD	1.15 [0.94;1.41]	1.15 [0.94;1.41]	1.00 [0.99;1.01]	0.6 [-5.9;9.6]	72863
	Stroke	0.92 [0.78;1.08]	0.91 [0.78;1.07]	1.00 [0.99;1.01]	-2.6 [-25.3;28.8]	72819
B. Father's occupational position (adj. adult occ.)						
Men	CHD	**1.17 [1.01;1.35]**	**1.17 [1.01;1.35]**	1.00 [0.99;1.01]	0.1 [-1;1.7]	36987
	Stroke	1.00 [0.76;1.32]	1.00 [0.76;1.32]	1.00 [0.99;1.01]	-153.1 [-21.6;19.7]	36759
Women	CHD	1.12 [0.91;1.37]	1.12 [0.91;1.37]	1.00 [0.99;1.01]	0.6 [-7;9.2]	72863
	Stroke	0.91 [0.77;1.08]	0.91 [0.77;1.08]	1.00 [0.99;1.01]	-2.1 [-25.6;14.6]	72819
C. Adult occupational position						
Men	CHD	**1.38 [1.06;1.75]**	**1.38 [1.07;1.76]**	1.00 [0.98;1.02]	-0.3 [-8.7;8.5]	36987
	Stroke	1.04 [0.61;1.69]	1.02 [0.60;1.65]	1.03 [0.99;1.07]	63.5 [-184.5;188.5]	36759
Women	CHD	**1.59 [1.14;2.22]**	**1.59 [1.13;2.21]**	1.01 [0.98;1.01]	1.4 [-0.3;5.8]	72863
	Stroke	1.14 [0.83;1.53]	1.13 [0.82;1.53]	1.00 [0.99;1.01]	3.3 [-30.4;30.1]	72819

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

A. Association between father's occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors

B. Association between father's occupational position and CVD, adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors

C. Association between adult occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors

MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by long sleep duration (**bold,** significant associations/mediation)

Supplementary Table 2: Association between father's occupational position and sleep duration based on individual cohort data, unadjusted for adult occupational position

			OR (95 %CI) [a]	P-value	N
Constances	**Men**	Short sleep (0h-6h)	1.25 [1.09;1.43]	0.001	24026
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.99 [0.88;1.12]	0.926	
	Women	Short sleep (0h-6h)	1.38 [1.21;1.57]	<0.001	26437
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.98 [0.89;1.08]	0.703	
GAZEL	**Men**	Short sleep (0h-6h)	1.05 [0.84;1.30]	0.683	6701
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1 [0.86;1.16]	0.974	
	Women	Short sleep (0h-6h)	1.02 [0.74;1.41]	0.909	2059
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.17 [0.87;1.57]	0.296	
E3N	**Women**	Short sleep (0h-6h)	1.22 [1.03;1.46]	0.024	39258
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.10 [1.02;1.18]	0.014	
Whitehall II	**Men**	Short sleep (0h-6h)	1.00 [0.65;1.53]	0.997	3117
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.66 [0.60;4.60]	0.333	
	Women	Short sleep (0h-6h)	1.48 [0.80;2.75]	0.215	1239
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.51 [0.16;1.61]	0.252	
ELSA	**Men**	Short sleep (0h-6h)	1.16 [0.71;1.89]	0.543	1694
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.13 [0.65;1.96]	0.659	
	Women	Short sleep (0h-6h)	0.91 [0.65;1.28]	0.599	2144
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.16 [0.73;1.84]	0.537	
COLAUS	**Men**	Short sleep (0h-6h)	1.21 [0.71;2.08]	0.486	1079
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.05 [0.36;3.10]	0.927	
	Women	Short sleep (0h-6h)	1.59 [0.90;2.79]	0.108	1149
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.95 [0.46;1.95]	0.888	
SKIPOGH	**Men**	Short sleep (0h-6h)	1.09 [0.42;2.82]	0.862	422
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	4.4 [1.06;18.25]	0.041	
	Women	Short sleep (0h-6h)	2.07 [0.85;5.02]	0.109	432
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.94 [0.28;3.19]	0.918	
EPIPORTO	**Men**	Short sleep (0h-6h)	2.21 [0.46;10.61]	0.320	584
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.77 [0.43;1.39]	0.390	
	Women	Short sleep (0h-6h)	19.04 [2.83;128.12]	0.002	864
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.82 [0.50;1.33]	0.418	

OR, odds ratio; CI, confidence interval

a Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours, and health behaviors

Supplementary Table 3: Association between father's occupational position and sleep duration based on individual cohort data, adjusted for adult occupational position

			OR (95 %CI) [a]	P-value	N
Constances	**Men**	Short sleep (0h-6h)	1.15 [1.01;1.32]	0.042	24026
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.94 [0.84;1.06]	0.336	
	Women	Short sleep (0h-6h)	1.26 [1.11;1.44]	<0.001	26437
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.95 [0.86;1.06]	0.353	
GAZEL	**Men**	Short sleep (0h-6h)	1.05 [0.85;1.30]	0.640	6701
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.00 [0.86;1.16]	0.985	
	Women	Short sleep (0h-6h)	1.01 [0.73;1.40]	0.949	2059
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.18 [0.88;1.58]	0.277	
E3N	**Women**	Short sleep (0h-6h)	1.21 [1.02;1.45]	0.029	39258
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.10 [1.02;1.19]	0.012	
Whitehall II	**Men**	Short sleep (0h-6h)	0.94 [0.61;1.45]	0.771	3117
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.56 [0.56;4.36]	0.400	
	Women	Short sleep (0h-6h)	1.36 [0.73;2.55]	0.334	1239
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.45 [0.14;1.43]	0.177	
ELSA	**Men**	Short sleep (0h-6h)	1.10 [0.67;1.80]	0.702	1694
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.04 [0.60;1.80]	0.899	
	Women	Short sleep (0h-6h)	0.84 [0.59;1.18]	0.314	2144
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.13 [0.71;1.81]	0.598	
COLAUS	**Men**	Short sleep (0h-6h)	1.05 [0.60;1.85]	0.866	1079
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.01 [0.33;3.07]	0.989	
	Women	Short sleep (0h-6h)	1.41 [0.79;2.50]	0.248	1149
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.00 [0.49;2.07]	0.992	
SKIPOGH	**Men**	Short sleep (0h-6h)	1.06 [0.41;2.75]	0.906	422
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	4.37 [1.05;18.15]	0.042	
	Women	Short sleep (0h-6h)	1.69 [0.68;4.19]	0.259	432
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.95 [0.28;3.28]	0.935	
EPIPORTO	**Men**	Short sleep (0h-6h)	2.38 [0.49;11.46]	0.280	584
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.69 [0.38;1.27]	0.234	
	Women	Short sleep (0h-6h)	18.86 [2.79;127.28]	0.003	864
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.81 [0.50;1.32]	0.399	

OR, odds ratio; CI, confidence interval

a Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for adult occupational position age, cohort, study period, flexible working hours, and health behaviors

Supplementary Table 4: Association between adult occupational position and sleep duration based on individual cohort data

			OR (95 %CI) [a]	P-value	N
Constances	**Men**	Short sleep (0h-6h)	2.73 [2.17;3.43]	<0.001	24026
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.98 [1.60;2.44]	<0.001	
	Women	Short sleep (0h-6h)	2.39 [1.95;2.93]	<0.001	26437
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.31 [1.11;1.55]	0.002	
GAZEL	**Men**	Short sleep (0h-6h)	0.68 [0.40;1.17]	0.163	6701
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.06 [0.73;1.54]	0.756	
	Women	Short sleep (0h-6h)	1.26 [0.66;2.42]	0.490	2059
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.84 [0.46;1.54]	0.567	
E3N	**Women**	Short sleep (0h-6h)	1.39 [1.00;1.94]	0.049	39258
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.88 [0.75;1.03]	0.100	
Whitehall II	**Men**	Short sleep (0h-6h)	2.58 [1.38;4.82]	0.003	3117
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	2.74 [0.73;10.27]	0.135	
	Women	Short sleep (0h-6h)	2.34 [0.80;6.82]	0.119	1239
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	4.04 [0.37;43.64]	0.250	
ELSA	**Men**	Short sleep (0h-6h)	1.95 [0.94;4.05]	0.075	1694
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	3.15 [1.29;7.71]	0.012	
	Women	Short sleep (0h-6h)	2.68 [1.58;4.54]	<0.001	2144
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.32 [0.66;2.66]	0.429	
COLAUS	**Men**	Short sleep (0h-6h)	2.91 [1.19;7.11]	0.019	1079
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.37 [0.26;7.31]	0.716	
	Women	Short sleep (0h-6h)	4.55 [1.58;13.14]	0.005	1149
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.58 [0.18;1.85]	0.354	
SKIPOGH	**Men**	Short sleep (0h-6h)	2.31 [0.42;12.65]	0.335	422
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.38 [0.15;12.73]	0.778	
	Women	Short sleep (0h-6h)	11.42 [2.37;55.08]	0.002	432
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	0.88 [0.14;5.53]	0.891	
EPIPORTO	**Men**	Short sleep (0h-6h)	0.70 [0.11;4.36]	0.702	584
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	2.59 [1.02;6.56]	0.046	
	Women	Short sleep (0h-6h)	1.71 [0.27;10.79]	0.569	864
		Normal sleep (6h-8.5h) (ref.)	1.00		
		Long sleep (>8.5h)	1.08 [0.43;2.68]	0.874	

OR, odds ratio; CI, confidence interval

a Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours, and health behaviors

Supplementary Table 5: Association between sleep duration and cardiovascular disorders based on individual cohort data

			Men			Women		
Constances			**OR (95%CI) [a]**	**P-value [b]**	**N**	**OR (95%CI) [a]**	**P-value [b]**	**N**
	Short sleep (0h-6h)	CHD	1.53 [1.18;1.99]	0.001	23534	1.58 [0.88;2.83]	0.124	25913
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		0.90 [0.69;1.17]	0.433		1.15 [0.63;2.10]	0.645	
	Short sleep (0h-6h)	Stroke	0.96 [0.59;1.57]	0.874	23522	1.51 [0.97;2.35]	0.069	25915
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		1.5 [1.06;2.13]	0.021		0.95 [0.59;1.53]	0.843	
GAZEL								
	Short sleep (0h-6h)	CHD	1.44 [1.06;1.96]	0.020	6701	***	***	2059
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		1.05 [0.82;1.34]	0.715		1.37 [0.15;12.54]	0.778	
	Short sleep (0h-6h)	Stroke	1.25 [0.60;2.64]	0.550	6515	1.04 [0.23;4.60]	0.961	2030
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		0.67 [0.33;1.35]	0.257		1.26 [0.36;4.41]	0.716	
E3N								
	Short sleep (0h-6h)	CHD				1.69 [1.10;2.59]	0.017	39258
	Normal sleep (6h-8.5h) (ref.)					1.00		
	Long sleep (>8.5h)					1.3 [1.03;1.63]	0.025	
	Short sleep (0h-6h)	Stroke				1.46 [1.03;2.05]	0.032	39258
	Normal sleep (6h-8.5h) (ref.)					1.00		
	Long sleep (>8.5h)					1.31 [1.11;1.55]	0.001	
Whitehall II								
	Short sleep (0h-6h)	CHD	1.98 [1.37;2.85]	<0.001	3117	1.52 [0.95;2.43]	0.082	1239
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		0.44 [0.13;1.45]	0.177		0.88 [0.26;3.02]	0.837	
	Short sleep (0h-6h)	Stroke	2.17 [0.47;10.09]	0.322	3117	5.64 [0.30;104.89]	0.246	1239
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		3.91 [0.48;31.65]	0.201		***	***	
ELSA								
	Short sleep (0h-6h)	CHD	1.84 [1.24;2.73]	0.003	1555	1.49 [1.03;2.15]	0.035	1956
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		1.50 [0.94;2.39]	0.087		0.89 [0.51;1.53]	0.670	
	Short sleep (0h-6h)	Stroke	0.94 [0.47;1.91]	0.873	1524	0.74 [0.41;1.33]	0.317	1937
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		2.41 [1.33;4.35]	0.004		0.67 [0.31;1.45]	0.314	
COLAUS								
	Short sleep (0h-6h)	CHD	1.35 [0.61;2.98]	0.461	1074	0.74 [0.17;3.19]	0.683	1145
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		0.95 [0.2;4.41]	0.948		0.99 [0.22;4.47]	0.988	
	Short sleep (0h-6h)	Stroke	4.99 [1.16;21.43]	0.031	1075	0.98 [0.12;7.81]	0.987	1146
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		17.49	0.001		1.35 [0.17;11.01]	0.777	
SKIPOGH								
	Short sleep (0h-6h)	CHD	1.56 [0.3;8.24]	0.599	422	1.47 [0.15;14.46]	0.743	432
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		0.69 [0.07;6.49]	0.742		***	***	
	Short sleep (0h-6h)	Stroke	5.07 [0.87;29.69]	0.072	422	***	***	432
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		2.74 [0.25;30.61]	0.412		***	***	
EPIPORTO								
	Short sleep (0h-6h)	CHD	2.85 [0.86;9.44]	0.087	584	2.12 [0.65;6.89]	0.210	861
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		1.07 [0.54;2.12]	0.840		1.55 [0.78;3.1]	0.212	
	Short sleep (0h-6h)	Stroke	***	***	584	1.08 [0.13;8.75]	0.944	862
	Normal sleep (6h-8.5h) (ref.)		1.00			1.00		
	Long sleep (>8.5h)		1.63 [0.57;4.64]	0.360		1.66 [0.63;4.37]	0.301	

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

a Logistic regression for the association between three category sleep duration (categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and CVD (outcome), adjusted for age, study period, flexible working hours, and health behaviors
*** OR could not be compute due to lack of statistical power

Supplementary Table 6: Counterfactual mediation estimates for the association between father's occupational position and cardiovascular disorders, mediated by short sleep duration (<6h/n), using individual cohort data (unadjusted for adult occupational position)

		MTE-OR (95%CI)	NDE-OR (95%CI)	NIE-OR (95%CI)	PM (95%CI)	N
Constances						
Men	CHD	**1.33 [1.02;1.75]**	**1.32 [1.01;1.73]**	1.01 [1;1.02]	2.6 [-1.5;16.1]	23534
	Stroke	0.81 [0.53;1.2]	0.81 [0.53;1.2]	1 [0.99;1.01]	0.7 [-18.7;22.9]	23522
Women	CHD	0.73 [0.38;1.38]	0.71 [0.37;1.35]	1.02 [0.99;1.07]	-5.9 [-81.5;64.6]	25913
	Stroke	1.12 [0.72;1.7]	1.1 [0.71;1.68]	1.01 [0.99;1.04]	12.4 [-94;83.7]	25915
GAZEL						
Men	CHD	1.1 [0.89;1.39]	1.1 [0.89;1.39]	1 [0.99;1.01]	1.3 [-20.1;29.5]	6701
	Stroke	1.41 [0.83;2.49]	1.4 [0.83;2.49]	1 [0.99;1.02]	0.7 [-11.7;17.4]	6515
Women	CHD	***	***	***	***	2059
	Stroke	***	***	***	***	2030
E3N						
Women	CHD	1.11 [0.84;1.5]	1.11 [0.84;1.49]	1.00 [0.99;1.01]	4 [-33.5;35.1]	39258
	Stroke	0.86 [0.69;1.07]	0.85 [0.69;1.06]	1.00 [0.99;1.01]	-2.9 [-29;20.9]	39258
Whitehall II						
Men	CHD	1.07 [0.76;1.5]	1.07 [0.76;1.49]	1 [0.97;1.02]	-0.1 [-68.5;71.5]	3117
	Stroke	***	***	***	***	3117
Women	CHD	**1.75 [1.06;3.06]**	**1.73 [1.04;3.02]**	1.02 [0.99;1.06]	3.6 [-4.8;25.7]	1239
	Stroke	***	***	***	***	1239
ELSA						
Men	CHD	1.48 [0.92;2.48]	1.47 [0.91;2.44]	1.01 [0.98;1.05]	2.7 [-18.4;28.6]	1555
	Stroke	1.04 [0.48;2.41]	1.04 [0.48;2.4]	1 [0.98;1.04]	2.7 [-38.8;33]	1524
Women	CHD	1.46 [0.88;2.43]	1.47 [0.9;2.44]	0.99 [0.96;1.02]	-1.6 [-30.3;22.1]	1956
	Stroke	0.67 [0.35;1.3]	0.66 [0.35;1.29]	1 [0.98;1.04]	-0.6 [-20.6;15.6]	1937
COLAUS						
Men	CHD	0.79 [0.4;1.56]	0.79 [0.39;1.56]	1 [0.97;1.06]	-0.8 [-41.3;44.9]	1074
	Stroke	***	***	***	***	1075
Women	CHD	0.86 [0.3;2.54]	0.84 [0.29;2.46]	1.02 [0.97;1.19]	-12.8 [-90.9;95.9]	1145
	Stroke	2.14 [0.51;10.49]	2.17 [0.49;10.58]	0.99 [0.96;1.06]	-2.8 [-16.4;14.9]	1146
SKIPOGH						
Men	CHD	1.7 [0.21;17.14]	1.67 [0.2;16.28]	1.02 [0.73;1.61]	5.4 [-144.7;138.9]	422
	Stroke	1.57 [0.17;23.91]	1.57 [0.16;24.49]	1 [0.78;1.18]	1.4 [-94.8;55.5]	422
Women	CHD	***	***	***	***	432
	Stroke	***	***	***	***	432
EPIPORTO						
Men	CHD	0.94 [0;2.88]	0.9 [0;2.72]	1.05 [0.97;1.26]	-80.3 [-135.6;142.7]	584
	Stroke	***	***	***	***	584
Women	CHD	5.98 [0.83;96.9]	5.5 [0.72;91.95]	1.09 [0.95;1.4]	9.7 [-22.9;70.2]	861
	Stroke	***	***	***	***	862

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease
Association between father's occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors
MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by short sleep duration (bold, significant associations/mediation)
*** OR could not be compute due to lack of statistical power

Supplementary Table 7: Counterfactual mediation estimates for the association between father's occupational position and cardiovascular disorders, mediated by short sleep duration (<6h/n), using individual cohort data (adjusted for adult occupational position)

		MTE-OR (95%CI)	NDE-OR (95%CI)	NIE-OR (95%CI)	PM (95%CI)	N
Constances						
Men	CHD	1.3 [1;1.71]	1.29 [0.99;1.7]	1.00 [0.99;1.01]	1.7 [-1.6;13.8]	23534
	Stroke	0.79 [0.52;1.17]	0.79 [0.52;1.18]	1 [0.99;1.01]	0.5 [-11.7;12.8]	23522
Women	CHD	0.72 [0.37;1.37]	0.7 [0.36;1.34]	1.02 [0.99;1.05]	-4 [-51.1;42.8]	25913
	Stroke	1.12 [0.71;1.74]	1.11 [0.7;1.72]	1.01 [1;1.03]	9 [-59.7;89.1]	25915
GAZEL						
Men	CHD	1.1 [0.89;1.38]	1.1 [0.89;1.38]	1 [0.99;1.01]	1.5 [-27.9;24.1]	6701
	Stroke	1.41 [0.83;2.5]	1.41 [0.84;2.48]	1 [0.99;1.02]	0.7 [-10.8;18.7]	6515
Women	CHD	***	***	***	***	2059
	Stroke	***	***	***	***	2030
E3N						
Women	CHD	1.1 [0.83;1.47]	1.1 [0.83;1.47]	1.00 [0.99;1.01]	4.3 [-32.6;49.9]	39258
	Stroke	0.86 [0.69;1.06]	0.85 [0.69;1.06]	1.00 [0.99;1.01]	-2.7 [-27.7;20.2]	39258
Whitehall II						
Men	CHD	1.03 [0.73;1.44]	1.03 [0.73;1.45]	1 [0.97;1.02]	-8.8 [-76.6;82.4]	3117
	Stroke	***	***	***	***	3117
Women	CHD	**1.73 [1.01;3.11]**	**1.71 [1.00;3.05]**	1.01 [0.98;1.05]	2.9 [-9;25.1]	1239
	Stroke	***	***	***	***	1239
ELSA						
Men	CHD	1.49 [0.91;2.51]	1.48 [0.91;2.47]	1.01 [0.97;1.05]	1.8 [-21.7;30.9]	1555
	Stroke	1.09 [0.51;2.51]	1.09 [0.51;2.51]	1.00 [0.98;1.03]	1.2 [-42.7;40.6]	1524
Women	CHD	1.4 [0.85;2.35]	1.41 [0.86;2.36]	0.99 [0.95;1.01]	-3.2 [-51.9;25]	1956
	Stroke	0.68 [0.35;1.36]	0.68 [0.35;1.34]	1.01 [0.98;1.05]	-1.2 [-25.5;24.2]	1937
COLAUS						
Men	CHD	0.68 [0.32;1.4]	0.68 [0.31;1.4]	1 [0.96;1.04]	-0.1 [-24.3;33.4]	1074
	Stroke	***	***	***	***	1075
Women	CHD	0.74 [0.25;2.36]	0.73 [0.24;2.33]	1.01 [0.97;1.15]	-3.8 [-71.5;52.2]	1145
	Stroke	2 [0.35;11.48]	2.02 [0.35;11.55]	0.99 [0.96;1.04]	-2.3 [-12.2;11.2]	1146
SKIPOGH						
Men	CHD	1.57 [0.17;15.32]	1.54 [0.17;15.29]	1.02 [0.71;1.59]	4.2 [-145.3;146.4]	422
	Stroke	2 [0.14;58.23]	1.99 [0.13;58.23]	1 [0.73;1.19]	0.6 [-104.7;59.7]	422
Women	CHD	***	***	***	***	432
	Stroke	***	***	***	***	432
EPIPORTO						
Men	CHD	0.97 [0;3.09]	0.92 [0;2.82]	1.05 [0.97;1.27]	-154.6 [-130.3;148.7]	584
	Stroke	***	***	***	***	584
Women	CHD	6.07 [0.76;89.89]	5.58 [0.71;82.78]	1.09 [0.95;1.4]	9.5 [-31.3;65.7]	861
	Stroke	***	***	***	***	862

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease
Association between father's occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors
MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by short sleep duration (bold, significant associations/mediation)
*** OR could not be compute due to lack of statistical power

Supplementary Table 8: Counterfactual mediation estimates for the association between adult occupational position and cardiovascular disorders, mediated by short sleep duration (<6h/n), using individual cohort data

		MTE-OR (95%CI)	NDE-OR (95%CI)	NIE-OR (95%CI)	PM (95%CI)	N
Constances						
Men	CHD	1.49 [0.93;2.26]	1.43 [0.9;2.2]	1.04 [0.99;1.09]	11.5 [-24.3;70.9]	23534
	Stroke	1.46 [0.71;2.9]	1.47 [0.71;2.93]	0.99 [0.94;1.06]	-2.5 [-83.7;65.8]	23522
Women	CHD	1.11 [0.37;2.88]	1.07 [0.35;2.77]	1.03 [0.97;1.13]	31.5 [-94.6;111.3]	25913
	Stroke	1.08 [0.55;2.16]	1.05 [0.53;2.14]	1.03 [0.98;1.09]	38.7 [-159.4;161.7]	25915
GAZEL						
Men	CHD	1.32 [0.75;2.17]	1.34 [0.76;2.22]	0.99 [0.94;1.01]	-5.8 [-70.6;44.9]	6701
	Stroke	0.98 [0.16;3.2]	0.99 [0.17;3.4]	0.99 [0.87;1.04]	47.3 [-58.4;44.5]	6515
Women	CHD	***	***	***	***	2059
	Stroke	***	***	***	***	2030
E3N						
Women	CHD	1.58 [0.89;2.54]	1.57 [0.89;2.54]	1.01 [1;1.03]	1.5 [-6.7;16]	39258
	Stroke	1.1 [0.71;1.62]	1.09 [0.71;1.61]	1 [1;1.02]	4.6 [-45.4;32.1]	39258
Whitehall II						
Men	CHD	**1.89 [1.18;3.22]**	**1.74 [1.09;2.82]**	1.08 [0.99;1.34]	16.4 [-2.2;53.1]	3117
	Stroke	***	***	***	***	3117
Women	CHD	1.33 [0.56;3.6]	1.31 [0.54;3.56]	1.01 [0.96;1.12]	5.6 [-67.6;80.8]	1239
	Stroke	***	***	***	***	1239
ELSA						
Men	CHD	0.91 [0.39;1.97]	0.82 [0.35;1.81]	1.1 [0.99;1.32]	-90.1 [-332.6;328.9]	1555
	Stroke	0.41 [0.09;1.33]	0.38 [0.08;1.23]	1.08 [0.95;1.39]	-5.1 [-83.9;51.1]	1524
Women	CHD	1.48 [0.72;3.02]	1.46 [0.71;2.95]	1.01 [0.93;1.13]	4.1 [-77.7;82.5]	1956
	Stroke	0.76 [0.24;2.05]	0.78 [0.25;2.11]	0.97 [0.88;1.11]	10.5 [-108.9;158.3]	1937
COLAUS						
Men	CHD	2.16 [0.67;7.54]	2.11 [0.63;7.47]	1.02 [0.94;1.16]	3.8 [-48.9;68.6]	1074
	Stroke	***	***	***	***	1075
Women	CHD	3.28 [0.57;40.26]	3.32 [0.54;39.44]	0.99 [0.93;1.16]	-1.7 [-26.8;41.5]	1145
	Stroke	1.5 [0.13;36.71]	1.49 [0.11;34.27]	1.01 [0.97;1.35]	2.5 [-69.7;100]	1146
SKIPOGH						
Men	CHD	6.97 [0.17;12.4]	5.88 [0.14;7.9]	1.19 [0.8;3.18]	18.3 [-59.2;124]	422
	Stroke	0.15 [0;467.87]	0.1 [0;107.38]	1.57 [0.67;7.25]	-6.6 [-193.8;198.3]	422
Women	CHD	***	***	***	***	432
	Stroke	***	***	***	***	432
EPIPORTO						
Men	CHD	0.78 [0.14;4.03]	0.82 [0.14;4.45]	0.96 [0.59;1.24]	14.8 [-203.9;214.3]	584
	Stroke	1.46 [0.05;208.59]	1.46 [0.05;208.59]	1 [1;1]	0 [0;0]	584
Women	CHD	0.67 [0.03;22.89]	0.66 [0.03;20.95]	1.01 [0.91;1.3]	-2.3 [-42.3;63.6]	861
	Stroke	***	***	***	***	862

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease
Association between adult occupational position and CVD, adjusted for age, cohort, study period, flexible working hours and health behaviors
MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by short sleep duration
*** OR could not be compute due to lack of statistical power

Supplementary Table 9: Longitudinal association between occupational position at baseline, and cardiovascular disease occurrence in the Whitehall II study through waves 1 to 8

	Outcome	Incident number of events (w1-w8)	HR (95%CI) [a]	P-value
Men	CHD	1289	1.23 [1.03;1.46]	0.017
	Stroke	139	2.33 [1.41;3.86]	0.001
Women	CHD	661	1.24 [0.97;1.60]	0.090
	Stroke	71	1.36 [0.61;3.01]	0.449

HR, Hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disorders

a Cox proportional hazard regression model for the association between three adult occupational position (predictor-Lowest vs. Highest) and CVD through waves 1 to 8, adjusted for age, and health behaviors

Supplementary Table 10: Longitudinal association between sleep duration at baseline, and cardiovascular disease occurrence in the Whitehall II study through waves 1 to 8

	Predictor	Outcome	Incident number of events (w1-w8)	HR (95%CI) [a]	P-value
Men	Short sleep (0h-6h)	CHD	1285	1.49 [1.19;1.87]	0.001
	Normal sleep (6h-8.5h) (ref. predictor)			1.00	
	Long sleep (>8.5h)			1.25 [1.02;1.52]	0.048
	Short sleep (0h-6h)	Stroke	137	1.37 [0.68;2.72]	0. 371
	Normal sleep (6h-8.5h) (ref. predictor)			1.00	
	Long sleep (>8.5h)			1.19 [0.47;10.24]	0.798
Women	Short sleep (0h-6h)	CHD	659	1.16 [0.87;1.53]	0.304
	Normal sleep (6h-8.5h) (ref. predictor)			1.00	
	Long sleep (>8.5h)			0.98 [0.59;1.69]	0.686
	Short sleep (0h-6h)	Stroke	71	0.77 [0.30;2.07]	0.614
	Normal sleep (6h-8.5h) (ref. predictor)			1.00	
	Long sleep (>8.5h)			***	***

HR, Hazard ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disorders

a Cox regression model for the association between three cat. sleep duration (wave 1- categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and CVD through waves 1 to 8, adjusted for age, and health behaviors

*** Insufficient statistical power

Supplementary Table 11: Association between SEP indicators and sleep duration based on pooled, imputed cohort data

Men		**OR (95 %CI)**	***P*-value**
A. Father's occupational position (unadj. adult occ.)	Short sleep (0h-6h)	1.17 [1.06;1.28]	0.002
	Normal sleep (6h-8.5h) (ref. outcome)	1.00	
	Long sleep (>8.5h)	1.02 [0.94;1.11]	0.623
B. Father's occupational position (adj. adult occ.)	Short sleep (0h-6h)	1.10 [0.99;1.21]	0.057
	Normal sleep (6h-8.5h) (ref. outcome)	1.00	
	Long sleep (>8.5h)	0.98 [0.90;1.06]	0.553
C. Adult occupational position	Short sleep (0h-6h)	2.45 [2.10;2.86]	<0.001
	Normal sleep (6h-8.5h) (ref. outcome)	1.00	
	Long sleep (>8.5h)	2.11 [1.82;2.44]	<0.001
Women			
A. Father's occupational position (unadj. adult occ.)	Short sleep (0h-6h)	1.34 [1.24;1.45]	<0.001
	Normal sleep (6h-8.5h) (ref. outcome)	1.00	
	Long sleep (>8.5h)	1.06 [1.01;1.12]	0.018
B. Father's occupational position (adj. adult occ.)	Short sleep (0h-6h)	1.26 [1.16;1.37]	<0.001
	Normal sleep (6h-8.5h) (ref. outcome)	1.00	
	Long sleep (>8.5h)	1.05 [1.00;1.11]	0.050
C. Adult occupational position	Short sleep (0h-6h)	2.27 [2.00;2.57]	<0.001
	Normal sleep (6h-8.5h) (ref. outcome)	1.00	
	Long sleep (>8.5h)	1.24 [1.14;1.35]	<0.001

OR, odds ratio; CI, confidence interval; occ., occupational position

A. Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

B. Multinomial logistic regression for the association between father's occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors

C. Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

Supplementary Table 12: Association between sleep duration and cardiovascular disorders based on pooled, imputed cohort data

			OR (95%CI) [a]	P-value
Men	Short sleep (0h-6h)	CHD	1.60 [1.40;1.82]	<0.001
	Normal sleep (6h-8.5h) (ref. predictor)		1.00	
	Long sleep (>8.5h)		1.07 [0.93;1.22]	0.357
	Short sleep (0h-6h)	Stroke	1.22 [0.94;1.59]	0.140
	Normal sleep (6h-8.5h) (ref. predictor)		1.00	
	Long sleep (>8.5h)		1.34 [1.07;1.68]	0.010
Women	Short sleep (0h-6h)	CHD	1.53 [1.28;1.83]	<0.001
	Normal sleep (6h-8.5h) (ref. predictor)		1.00	
	Long sleep (>8.5h)		1.19 [1.02;1.39]	0.026
	Short sleep (0h-6h)	Stroke	1.43 [1.19;1.73]	<0.001
	Normal sleep (6h-8.5h) (ref. predictor)		1.00	
	Long sleep (>8.5h)		1.22 [1.08;1.38]	0.002

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

[a] Logistic regression for the association between three category sleep duration (categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and cardiovascular disorders (outcome), adjusted for age, cohort , study period, flexible working hours, and health behaviors

Supplementary Table 13: Counterfactual mediation estimates for the association between adult occupational position and CHD mediated by short sleep duration (<6h/n), non-adjusted (A) and adjusted (B) for four sleep-quality indicators (Constances and GAZEL pooled data)

A. Unadjusted for sleep quality indicators	**MTE-OR (95%CI)**	**NDE-OR (95%CI)**	**NDE-OR (95%CI)**	**PM (95%CI)**	**N**
Men	**1.47 [1.05;2.07]**	**1.43 [1.02;2]**	**1.03 [1;1.07]**	**9.5 [0.2;49]**	30235
Women	0.92 [0.33;2.25]	0.9 [0.31;2.18]	1.03 [0.97;1.11]	-30.1 [-104.5;99]	27972
B. Adjusted for sleep quality indicators					
Men	1.36 [0.94;1.94]	1.35 [0.93;1.94]	1 [0.99;1.02]	1.8 [-10.3;23.1]	28358
Women	0.94 [0.3;2.54]	0.93 [0.3;2.53]	1 [0.98;1.05]	-7.6 [-42.6;33.5]	26185

A. Association between adult occupational position and CHD, adjusted for age, adult occupational position, cohort, study period, flexible working hours and health behaviors, unadjusted for sleep quality indicators

B. Association between adult occupational position and CHD, adjusted for age, cohort, study period, flexible working hours and health behaviors, additionally adjusted for four sleep quality indicators, namely "Difficulty falling asleep", "Difficulty waking up in the morning", "Waking up during the night", "Waking up too early" – sleep quality related beta coefficients (M1 and M2) are presented in Supplementary Table 5

MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by sleep duration (* significant mediation)

Supplementary Table 14: Sleep quality beta coefficients for mediation models 1-θ and 2-β (Annex 1), computed for the association between adult occupational position and CHD, mediated by sleep duration – (Constances and GAZEL pooled data)

	Difficulty falling asleep	**Difficulty waking up in the morning**	**Waking up during the night**	**Waking up too early**
[a] Men-M1: θ_4^c (95%CI)	**0.33 [0.05;0.6]**	0.01 [-0.31;0.29]	**0.2 [0.04;0.36]**	0.09 [-0.19;0.33]
[b] Men-M2: β_4^c (95%CI)	**0.98 [0.83;1.12]**	**0.31 [0.15;0.46]**	**0.4 [0.27;0.51]**	**1.5 [1.38;1.63]**
[a] Women-M1: θ_4^c (95%CI)	-0.24 [-1.16;0.48]	0.44 [-0.32;1.14]	0.08 [-0.59;0.66]	0.42 [-0.43;1.18]
[b] Women-M2: β_4^c (95%CI)	**1.01 [0.88;1.14]**	**0.23 [0.1;0.36]**	**0.57 [0.44;0.69]**	**1.51 [1.38;1.63]**

[a] M1. Logistic regression model for the association between SEP (main predictor) and CVD (binary outcome) (coefficient θ_1^{sep}), including sleep duration (θ_2^m- effect of sleep duration on CVD) , an interaction term between SEP and sleep duration (θ_3^{sep*m}), and major confounders (θ_4^c - age, cohort, study period, health behaviors, and flexible working hours)

[b] M2. Multinomial regression model for the association between SEP (main predictor) and sleep duration (categorical outcome) (β_1^{sep}), including the effect of major confounders (β_4^c - age, cohort, study period, health behaviors, and flexible working hours)

(**bold**, significant associations/mediation)

Supplementary Table 15: Summary of data acquisition methods across individual cohorts

	Constances	GAZEL	E3N	Whitehall II	ELSA	COLAUS	SKIPOGH	EPIPORTO
Father's occ.	SR	SR	SR	SR	SR	SR	SR	SR
Adult occ.	SR	**OA-WR**	SR	**OA-WR**	SR	SR	SR	SR
Sleep	SR	SR	SR	SR	SR	SR	SR	SR
CVD (history & baseline)	**OA**[a]	SR	**OA**[b]	**OA**[c]	SR	SR	SR	SR
Health behaviors	SR	SR	SR	SR	SR	SR	SR	SR

Occ., Occupational position; SR, Self-report; OA, Objective assessment; WR, Work registry; Health behaviors (smoking, alcohol intake, and sedentary behavior)
[a] Health-questionnaire filled in with a physician and by using participant's personal medical record at interview
[b] Complementary information related to medical history provided by participants' GP
[c] Thorough medical examination at interview and access to personal medical records

Supplementary Table 16: Association between adult occupational position and sleep duration among cohorts that included objectively assessed CHD events (A), and self-reported data (B)

Men – Adult occupational position (predictor)	Outcome	OR (95 %CI) [d]	*P*-value [d]	N
A. Objective assessment (CHD)	Short sleep (0h-6h)	2.72 [2.19;3.37]	<0.001	27143
	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.99 [1.62;2.45]	<0.001	
B. Self-reported data	Short sleep (0h-6h)	1.25 [0.88;1.79]	0.218	10480
	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.49 [1.10;2.02]	0.011	
Women - Adult occupational position (predictor)				
A. Objective assessment (CHD)	Short sleep (0h-6h)	2.08 [1.76;2.46]	<0.001	66934
	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.13 [1.01;1.26]	0.030	
B. Self-reported data	Short sleep (0h-6h)	2.38 [1.67;3.37]	<0.001	6648
	Normal sleep (6h-8.5h) (ref. outcome)	1.00		
	Long sleep (>8.5h)	1.05 [0.73;1.52]	0.790	

OR, odds ratio; CI, confidence interval

A. Constances, Whitehall II, and E3N (women) data

B. GAZEL, ELSA, COLAUS, SKIPOGH, and EPIPORTO

[d] Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

Supplementary Table 17: Association between sleep duration and CHD among cohorts that included objectively assessed CHD events (A), and self-reported data (B)

		Men			Women		
A. Objective assessment (CHD)	**Outcome**	**OR (95%CI) [d]**	**P-value [d]**	**N**	**OR (95%CI) [a]**	**P-value**	**N**
Short sleep (0h-6h)	**CHD**	1.67 [1.35;2.07]	<0.001	26651	1.64 [1.24;2.17]	<0.001	66410
Normal sleep (6h-8.5h) (ref. **predictor**)		1.00			1.00		
Long sleep (>8.5h)		0.89 [0.69;1.15]	0.365		1.27 [1.03;1.57]	0.026	
B. Self-reported data							
Short sleep (0h-6h)	**CHD**	1.61 [1.29;2.02]	<0.001	10336	1.47 [1.05;2.06]	0.023	6453
Normal sleep (6h-8.5h) (ref. **predictor**)		1.00			1.00		
Long sleep (>8.5h)		1.12 [0.91;1.37]	0.276		1.16 [0.79;1.71]	0.438	

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

A. Constances, Whitehall II, and E3N (women) data

B. GAZEL, ELSA, COLAUS, SKIPOGH, and EPIPORTO

[d] Logistic regression for the association between three cat. sleep duration (categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and CHD (outcome), adjusted for age, cohort, study period, flexible working hours and health behaviors

Supplementary Table 18: Counterfactual mediation estimates for the association between adult occupational position and CHD, mediated by short sleep duration among cohorts that included objectively assessed CHD events (A), and self-reported data (B)

Men - Adult SEP, short sleep, CHD	**MTE-OR (95%CI)**	**NDE-OR (95%CI)**	**NIE-OR (95%CI)**	**PM (95%CI)**	**N**
A. Objective assessment (CHD)	1.60 [1.14;2.24]	1.53 [1.09;2.15]	1.04 [1.01;1.1]	11.1 [1.3;37]	26651
B. Self-reported data	1.32 [0.89;1.93]	1.3 [0.87;1.91]	1.01 [0.99;1.05]	6 [-31.3;56.8]	10336
Women - Adult SEP, short sleep, CHD					
A. Objective assessment (CHD)	1.44 [0.94;2.14]	1.42 [0.93;2.11]	1.01 [0.99;1.04]	4.4 [-19.5;33.2]	66410
B. Self-reported data	1.49 [0.77;2.76]	1.48 [0.77;2.74]	1.01 [0.97;1.06]	2.1 [-37.8;46.8]	6453

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

A. Constances, Whitehall II, and E3N (women) data

B. GAZEL, ELSA, COLAUS, SKIPOGH, and EPIPORTO

MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and CHD which is mediated by short sleep duration

Supplementary Table 19: Association between education and sleep duration based on pooled cohort data

Men		**OR (95 %CI)** [a]	***P*-value**	**N**
Education (High, Middle, Low) [b]	Short sleep (0h-6h)	1.86 [1.46;2.36]	<0.001	20154
	Normal sleep (6h-8.5h) (ref. **outcome**)	1.00		
	Long sleep (>8.5h)	1.48 [1.17;1.87]	<0.001	
Women				
Education (High, Middle, Low) [b]	Short sleep (0h-6h)	1.94 [1.54;2.43]	<0.001	39218
	Normal sleep (6h-8.5h) (ref. **outcome**)	1.00		
	Long sleep (>8.5h)	1.5 [1.22;1.83]	<0.001	

OR, odds ratio; CI, confidence interval

[a] Multinomial logistic regression for the association between education (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

[b] Highest level of attained education was self-reported by study participants across cohorts according to 7-9 categories and further harmonized into three levels : High (Tertiary education - University), Middle (Higher secondary school), Low (Primary or lower secondary school)

Supplementary Table 20: Counterfactual mediation estimates for the association between education and CVD outcomes, mediated by short sleep duration, using pooled data

Education (High, Middle, Low) [a]	Outcome	MTE-OR (95%CI)	NDE-OR (95%CI)	NIE-OR (95%CI)	PM (95%CI)	N
Men	CHD	1.40 [1.21;1.65]	1.37 [1.18;1.60]	1.03 [1.01;1.05]	**9.2 [4.1;18.0]**	36802
	Stroke	1.37 [1.00;1.87]	1.36 [0.99;1.85]	1.01 [0.99;1.04]	3.5 [-9.8;28.8]	36575
Women	CHD	1.55 [1.22;2.00]	1.53 [1.20;1.97]	1.01 [1.00;1.03]	3.8 [-0.6;11.4]	71206
	Stroke	1.05 [0.84;1.33]	1.05 [0.84;1.32]	1.00 [0.99;1.02]	5.5 [-105.3;95.2]	71161

OR, odds ratio; CI, confidence interval; CVD, cardiovascular disorders; CHD, coronary heart disease

MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between education and cardiovascular disorders which is mediated by short sleep duration

[a] Highest level of attained education was self-reported by study participants across cohorts according to 7-9 categories and further harmonized into three levels : High (Tertiary education - University), Middle (Higher secondary school), Low (Primary or lower secondary school)

Supplementary Table 21: Association between adult occupational position and sleep duration based on pooled cohort data (model further adjusted for type 2 diabetes and obesity)

Men – Adult occupational position (predictor)	**OR (95 %CI) [a]**	***P*-value [a]**	**N**
Short sleep (0h-6h)	2.15 [1.78;2.59]	<0.001	35485
Normal sleep (6h-8.5h) (ref. **outcome**)	1.00		
Long sleep (>8.5h)	1.85 [1.55;2.2]	<0.001	
Women – Adult occupational position (predictor)			
Short sleep (0h-6h)	2.37 [1.97;2.84]	<0.001	32515
Normal sleep (6h-8.5h) (ref. **outcome**)	1.00		
Long sleep (>8.5h)	1.28 [1.1;1.49]	0.002	

OR, odds ratio; CI, confidence interval

a Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <6h/night; Normal: ≥6h-8.5h/night; Long: ≥8.5h/night), adjusted for age, cohort, study period, flexible working hours, health behaviors, type 2 diabetes, and obesity

Supplementary Table 22: Association between sleep duration and cardiovascular disorders based on pooled cohort data (model further adjusted for type 2 diabetes and obesity)

		Outcome	OR (95%CI) [a]	P-value [a]	N
Men	Short sleep (0h-6h)	**CHD**	1.55 [1.32;1.83]	<0.001	34974
	Normal sleep (6h-8.5h) (ref. **predictor**)		1.00		
	Long sleep (>8.5h)		0.99 [0.84;1.16]	0.870	
Women	Short sleep (0h-6h)	**CHD**	1.4 [1.04;1.89]	0.029	31951
	Normal sleep (6h-8.5h) (ref. **predictor**)		1.00		
	Long sleep (>8.5h)		1.2 [0.85;1.69]	0.305	

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

a Logistic regression for the association between three cat. sleep duration (categorical predictor-Short: <6h/night; Normal: ≥6h-8.5h/night; Long: ≥8.5h/night) and CVD (outcome), adjusted for age, cohort, study period, flexible working hours, health behaviors, type 2 diabetes, and obesity

Supplementary Table 23: Counterfactual mediation estimates for the association between adult occupational position and CHD, mediated by short sleep duration, using pooled data (model further adjusted for type 2 diabetes and obesity)

Adult occupational position (predictor) – CHD (outcome)	MTE-OR (95%CI)	NDE-OR (95%CI)	NIE-OR (95%CI)	PM (95%CI)	N
Men	1.22 [0.93;1.58]	1.18 [0.9;1.53]	1.03 [1.01;1.06]	17.9 [-110.5;153.4]	34974
Women	1.17 [0.68;1.99]	1.17 [0.68;2]	1 [0.97;1.04]	1.00 [-64.4;53.7]	31951

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

MTE: Marginal total effect (OR 95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between adult occupational position and cardiovascular disorders which is mediated by short sleep duration. Model adjusted for age, cohort, study period, flexible working hours, health behaviors, type 2 diabetes, and obesity

Supplementary Table 24: Association between adult occupational position and modified sleep duration (extreme thresholds) based on pooled cohort data

Men – Adult occupational position (predictor)	**OR (95 %CI) [a]**	***P*-value [a]**	**N**
Short sleep (0h-5h)	4.09 [2.95;5.66]	<0.001	37623
Normal sleep (5h-10h) (ref. **outcome**)	1.00		
Long sleep (>10h)	2.45 [1.8;3.33]	<0.001	
Women			
Short sleep (0h-5h)	3.35 [2.46;4.55]	<0.001	73582
Normal sleep (5h-10h) (ref. **outcome**)	1.00		
Long sleep (>10h)	1.52 [1.26;1.83]	<0.001	

OR, odds ratio; CI, confidence interval

[a] Multinomial logistic regression for the association between adult occupational position (predictor-Lowest vs. Highest) and three category sleep duration (outcome-Short: <5h/night; Normal: ≥5h-10/night; Long: ≥10h/night), adjusted for age, cohort, study period, flexible working hours and health behaviors

Supplementary Table 25: Association between modified sleep duration (extreme thresholds) based on pooled cohort

		Outcome	OR (95%CI) [a]	P-value [a]	N
Men	Short sleep (0h-5h)	**CHD**	1.96 [1.55;2.48]	<0.001	36987
	Normal sleep (5h-10h) (ref. **predictor**)		1.00		
	Long sleep (>10h)		1.07 [0.79;1.44]	0.675	
Women	Short sleep (0h-5h)	**CHD**	1.91 [1.41;2.61]	<0.001	72863
	Normal sleep (5h-10h) (ref. **predictor**)		1.00		
	Long sleep (>10h)		1.34 [1.00;1.8]	0.053	

OR, odds ratio; CI, confidence interval; CHD, coronary heart disease

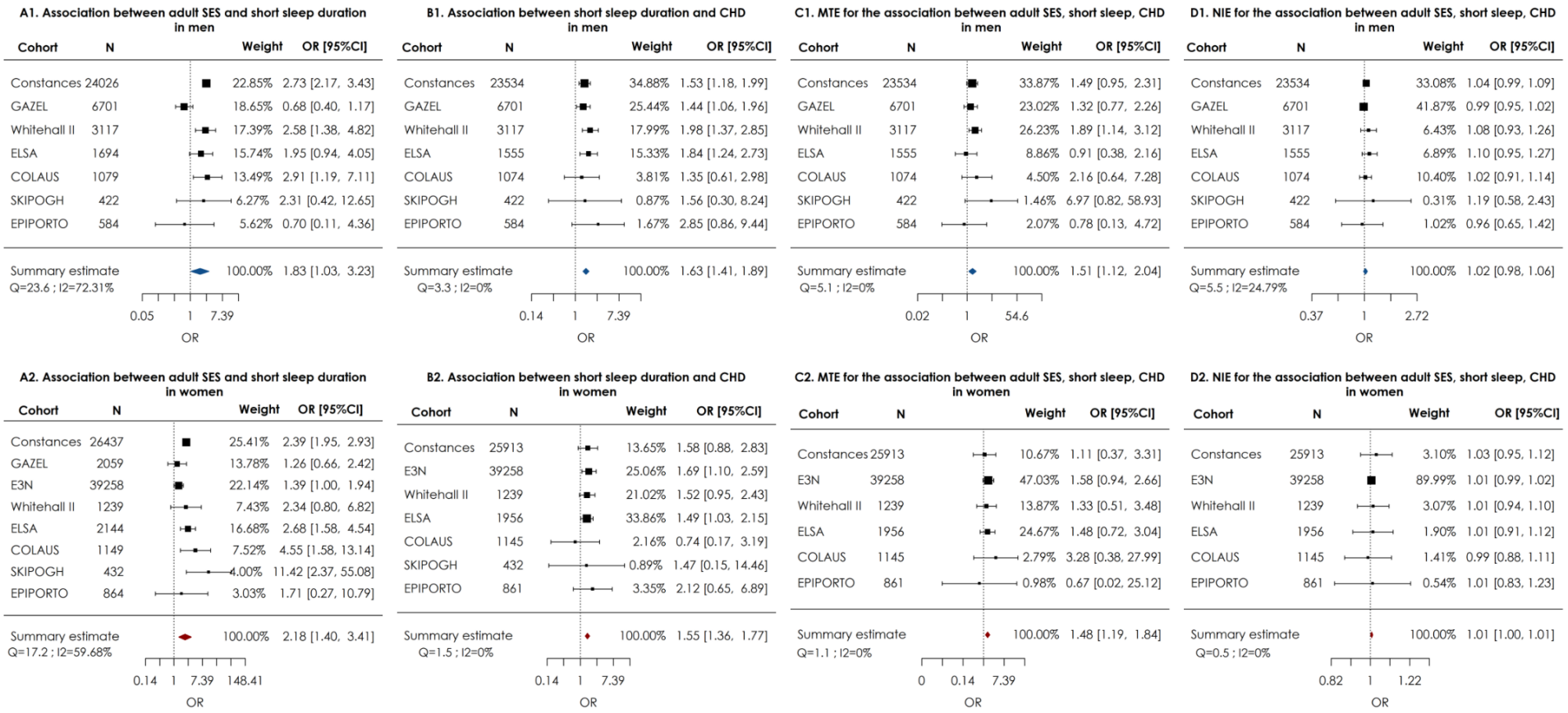
a Logistic regression for the association between three cat. sleep duration (categorical predictor-Short: <5h/night; Normal: ≥5h-10h/night; Long: ≥10h/night) and CVD (outcome), adjusted for age, cohort, study period, flexible working hours and health behaviors

Supplementary Table 26: Counterfactual mediation estimates for the association between adult occupational position and cardiovascular disorders, mediated by short sleep duration (<5h/n), and long sleep duration (>10h/n), using pooled cohort data

Mediator: Short sleep (0h-5h)	**MTE-OR (95%CI)**	**NDE-OR (95%CI)**	**NIE-OR (95%CI)**	**PM (95%CI)**	**N**
Men	1.42 [1.10;1.81]	1.39 [1.08;1.78]	1.02 [1.00;1.04]	6.5 [0.8;23.7]	36987
Women	1.54 [1.09;2.12]	1.54 [1.09;2.11]	1.00 [0.99;1.01]	0.9 [-0.5;5.1]	72863
Mediator: Long sleep (>10h)					
Men	1.40 [1.09;1.78]	1.40 [1.08;1.78]	1.00 [0.99;1.02]	0.7 [-3.4;8.0]	36987
Women	1.57 [1.12;2.17]	1.56 [1.11;2.15]	1.01 [0.99;1.02]	1.7 [-0.7;7.6]	72863

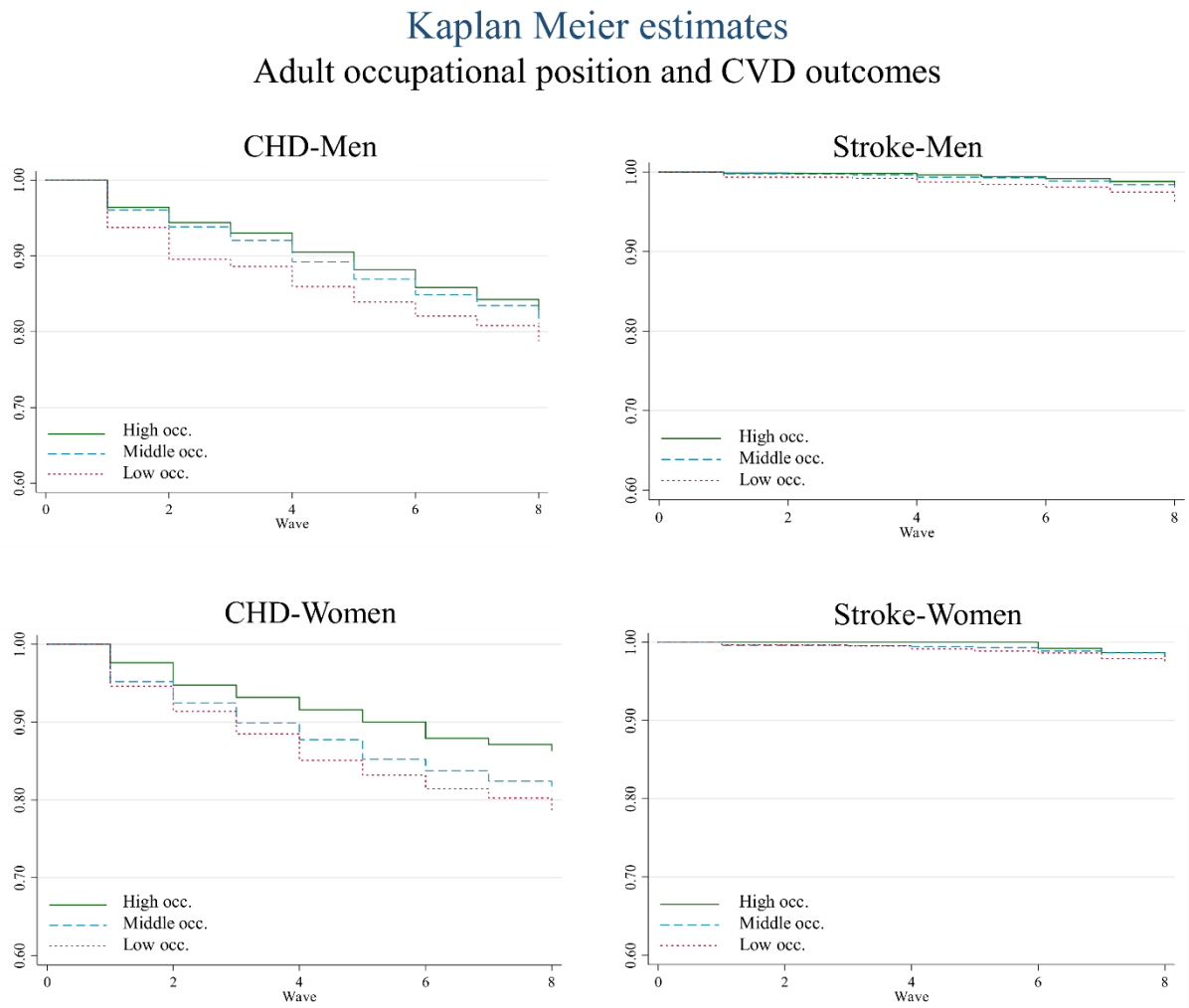
OR, odds ratio; CI, confidence interval; CHD, coronary heart disease
MTE: Marginal total effect (OR95%CI); NDE: Natural direct effect (OR 95%CI); NIE: Natural indirect effect (OR 95%CI); PM: Proportion of the association between occupational position and cardiovascular disorders which is mediated by sleep duration

Supplementary Figure 1: Random effect meta-analyses for associations between adult occupational position and sleep-duration (A), sleep duration and CHD, and MTE and NIE (mediation proxy) parameters for the associations between adult occupational position, short sleep duration, and CHD (C, D).



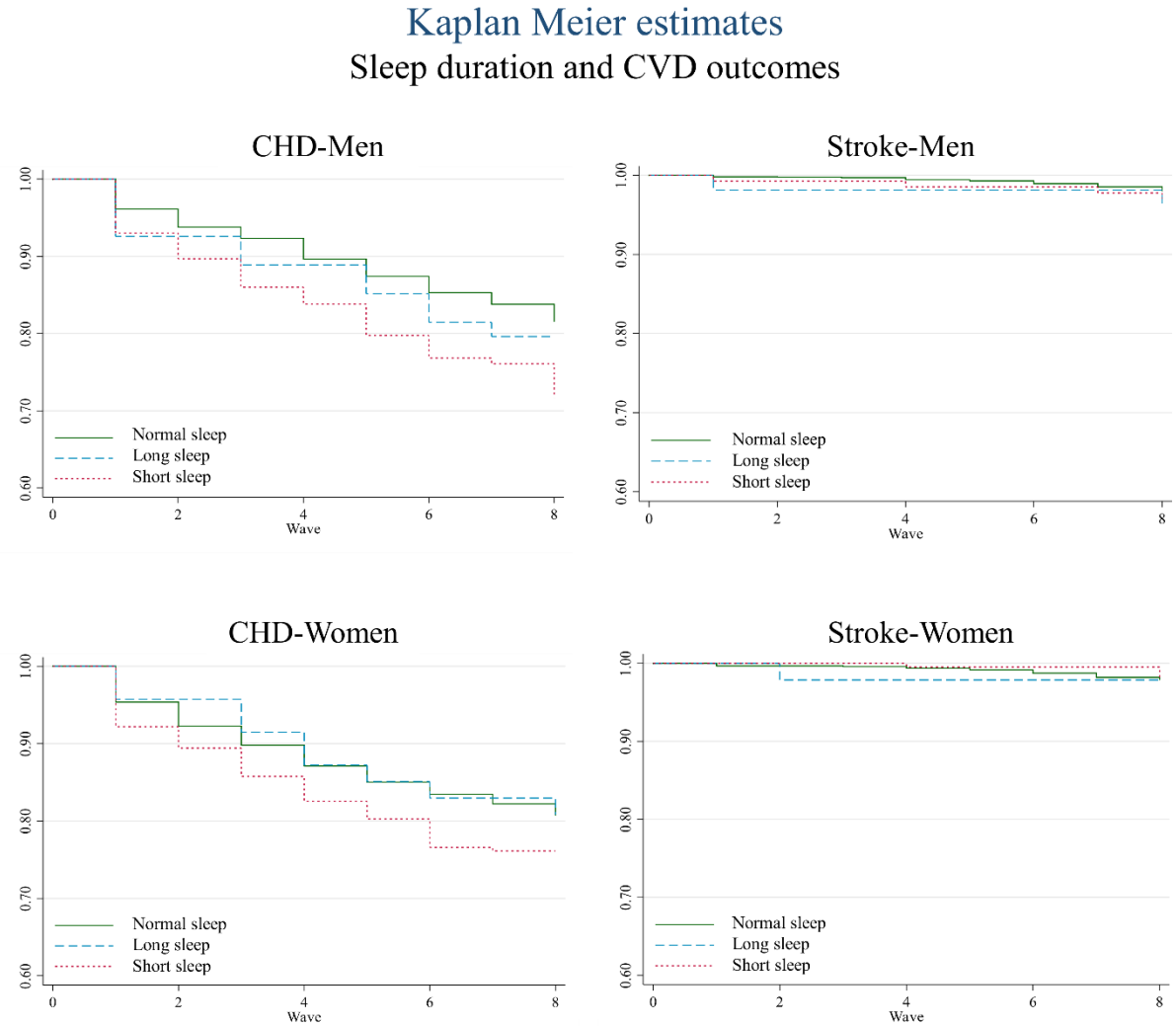
Q, Cochran's Q statistic for estimating heterogeneity, I2, heterogeneity index (%) based on Cochran's Q; MTE, Marginal total effect - proxy for the *total* effect of adult SEP on CHD; NIE, Natural indirect effect – proxy for the mediating effect of short sleep duration to the association between adult SEP, short sleep duration, and CHD

Supplementary Figure 2: Survival curves for the longitudinal association between adult occupational position at baseline (wave 1), and cardiovascular disease occurrence in the Whitehall II study through waves 1 to 8



CHD, coronary heart disease; occ., adult occupational position
a Cox proportional hazard regression model for the association between three adult occupational position (predictor-Lowest vs. Highest) and CVD through waves 1 to 8, adjusted for age, and health behaviors

Supplementary Figure 3: Survival curves for the longitudinal association between sleep duration at baseline (wave 1), and cardiovascular disease occurrence in the Whitehall II study through waves 1 to 8



CHD, coronary heart disease

a Cox regression model for the association between three cat. sleep duration (wave 1- categorical predictor-Short: <6h/night; Normal: ≥6h-8.5/night; Long: ≥8.5h/night) and CVD through waves 1 to 8, adjusted for age, and health behaviors

Annex 1: Formulas for the mediation models (M1, M2) and the calculation of Natural Direct Effect (NDE), Natural Indirect Effect (NIE), Marginal Total Effect (MTE), Proportion Mediated (PM)

M1: $CVD\ (main\ outcome) = \theta_1^{sep} + \theta_2^{m} + \theta_3^{sep*m} + \theta_4^{cov}$

M2: $Sleep\ duration\ (mediator) = \beta_1^{sep} + \beta_4^{cov}$

$$NDE = \frac{\exp\left(\theta_1^{sep} * a\right) * (1 + (\exp(\theta_2^{m} + \theta_3^{ses*m} * a^{*} + \beta_0 + \beta_4^{cov} * c)))}{\exp\left(\theta_1^{sep} * a^{*}\right) * (1 + (\exp(\theta_2^{m} + \theta_3^{ses*m} * a^{*} + \beta_0 + \beta_4^{cov} * c)))}$$

$$NIE = \frac{(1 + \exp\left(\beta_0 + \beta_1^{sep} * a^{*} + \beta_4^{cov} * c\right)) * (1 + \exp(\theta_2^{m} + \theta_3^{ses*m} * a + \beta_0 + \beta_1 * a + \beta_4^{cov} * c))}{(1 + \exp\left(\beta_0 + \beta_1^{sep} * a + \beta_4^{cov} * c\right)) * (1 + \exp(\theta_2^{m} + \theta_3^{ses*m} * a + \beta_0 + \beta_1 * a^{*} + \beta_4^{cov} * c))}$$

$$MTE = \exp(\log(NDE) + \log(NIE))$$

$$PM = (NDE * (NIE - 1))/(NDE * NIE - 1)$$

COV, Covariables (age, cohort, study period, health behaviors, flexible working hours; SEP: (Adult/Father's occupational position); M: mediator – sleep duration, SEP*M: Interaction term SEP * Mediator (Sleep duration); CVD, cardiovascular disorders;
NDE, Natural Direct Effect; NIE, Natural Indirect Effect; MTE, Marginal Total Effect, PM, Proportion Mediated
M1. Logistic regression model for the association between SEP (main predictor) and CVD (binary outcome) (coefficient θ_1^{sep}), including sleep duration (θ_2^{m}-effect of sleep duration on CVD) , an interaction term between SEP and sleep duration (θ_3^{sep*m}), and major confounders (θ_4^{c} - age, cohort, study period, health behaviors, and flexible working hours)
M2. Multinomial regression model for the association between SEP (main predictor) and sleep duration (categorical outcome) (β_1^{sep})

Annex 2: Assessment of sedentary behavior, type 2 diabetes, and obesity

Physical activity and sedentary behavior

Sedentary behavior was based on self-reported physical activity where participants reported the time they spent participating in a physical activity in and out of work (EPIPORTO), by rating their level of physical activity on a scale (SKIPOGH), by indicating the frequency of physical activity (SKIPOGH, CONSTANCES, GAZEL, E3N), or by using detailed questionnaires inquiring about the time, the frequency, the amount, and the type of physical activity (Whitehall II, COLAUS). These indicators were subsequently harmonized into a dichotomous "sedentary behavior" variable.

Type 2 diabetes and obesity

Type 2 diabetes status was available in seven cohorts (Constances, GAZEL, Whitehall II, SKIPOGH, ELSA, COLAUS, EPIPORTO), and defined based on self-report, a previous diagnosis of this disease by a physician, use of anti-diabetic medication, or having fasting blood glucose ≥ 7mmol/L or glycated hemoglobin (Hba1c) ≥ 6.5% at clinical visit. Obesity status was available in all eight cohorts, and was defined as having a body mass index (BMI) ≥ 30kg/m^2 at clinical visit, by dividing objectively measured weight (kilograms) by squared height (meters)

Chapter 3 Exploring the relation between life-course socioeconomic position and genome-wide CpG DNA methylation markers in a Swiss-population based study

Exploring the relation between life-course socioeconomic position and genome-wide CpG DNA methylation markers in a Swiss-population based study

Dusan Petrovic[1], Cristian Carmeli[1], Barbara Bodinier[2], Marc Chadeau-Hyam[2], Georg Ehret[3], Nasser Dhayat[4], Belen Ponte[5], Menno Pruijm[6], Emmanouil Dermitzakis[7], Murielle Bochud[1], Silvia Stringhini[1, 8]

1. Institute of Social and Preventive Medicine (IUMSP), Centre universitaire de médecine Générale et santé publique (UNISANTÉ), Lausanne, Switzerland
2. Centre for Environment and Health, School of Public Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK
3. Department of Cardiology, University Hospital of Geneva (HUG), Rue Gabrielle Perret-Gentil 4, 1205 Geneva, Switzerland
4. University Clinic for Nephrology, Hypertension and Clinical Pharmacology, Bern University Hospital, Bern, Switzerland
5. Department of Nephrology and Hypertension, University Hospital of Geneva, Geneva, Switzerland
6. Department of Nephrology and Hypertension, Lausanne University Hospital, Lausanne, Switzerland
7. Department of Genetic Medicine and Development, University of Geneva, Geneva, Switzerland
8. Unit of Population Epidemiology, Primary Care Division, Geneva University Hospital, Geneva, Switzerland

Correspondence:
Dr. Silvia Stringhini, e-mail: silvia.stringhini@unisante.ch
Address: Route de la Corniche 10, 1010 Lausanne, Switzerland
Telephone: +41 (0)21 314 26 14
FAX: +41 (0)21 314 73 73

Abstract

Background

Previous investigations have reported that adverse socioeconomic circumstances across the life-course lead to the alteration of major biological processes, eventually resulting in a higher disease risk and premature death. In particular, a low life-course socioeconomic position (SEP) has been associated with a modified epigenetic signature of loci involved in inflammation, the physiological response to stress, and other regulatory processes.

Methods

In this study, we investigated the association between nine indicators of SEP across the life-course and the differential methylation of 451'000 genome-wide CpG markers, using data from 690 adults included in a Swiss population-based study. We further examined the interrelations between the SEP-related CpGs, and the biological pathways in which the identified markers are involved.

Results

Three SEP indicators in adulthood were associated the differential methylation of 161 genome-wide CpG markers, whereby 156 CpGs were less methylated in people with low versus high SEP. Among the identified CpGs, a substantial proportion of markers were no longer associated with SEP upon accounting for health behaviors and cardiometabolic disorders. In addition, the identified CpGs were found to be involved in immune, inflammatory, and cancer-related processes.

Conclusion

Our results support the hypothesis that adverse socioeconomic circumstances may lead to the dysregulation of inflammatory processes, eventually resulting in the occurrence of serious chronic conditions such as atherosclerosis, diabetes, or cancer.

Introduction

Adverse socioeconomic conditions account for the most important determinants of ill health and premature mortality, however, the mechanisms underlying these associations are not fully understood [1-3]. To explain this relation, recent epidemiological research has been increasingly investigating the biological processes through which the social environment "gets embedded" under the skin, eventually altering the body's physiological functions and leading to disease [2]. Among the suggested biological pathways of the social embedding is the dysregulation of the Hypothalamus-Pituitary-Adrenal axis, aberrant inflammation, altered neural function and structure, and high allostatic load [2]. Moreover, the underlying molecular mechanism of modified epigenetic signature has been the object of particular attention in recent years [2, 4-7].

A modified epigenetic signature results from DNA methylation, whereby methyl groups are added to cytosines of CpG dinucleotides throughout the genome, eventually affecting gene expression [8, 9]. DNA methylation occurs as a natural regulatory process, but may also result from multiple environmental exposures, including cigarette smoking, physical exercise, environmental toxins, dietary exposures, as well as adversity and psychosocial factors [6, 10-13]. In the context of social epidemiology, former studies have suggested that chronic stress, inadequate nutrition, pollution, and other exposures resulting from poor socioeconomic circumstances across the life-course may alter the DNA methylation of selected loci involved in the regulation of many genes, including those regulating inflammation and other major processes, eventually leading to various conditions such as diabetes, atherosclerosis, or cancer [5, 6, 12, 14-16].

Despite these findings, a global understanding of socially driven DNA methylation changes and the subsequent occurrence of diseases is lacking. One of the main limitations of previous research is the focus on targeted approaches by examining epigenetic modifications occurring

in candidate genes, or in gene promoters, which restricts the relation between socioeconomic circumstances and DNA methylation to specific processes (i.e. inflammation, glucocorticoid signaling) and may introduce some bias [6]. Moreover, results from previous research have often been inconsistent in terms of socioeconomically induced DNA methylation changes, with some studies reporting increased methylation (hypermethylation), whereas others found decreased methylation of candidate genes or regions (hypomethylation) [5, 6, 17].

In this study, we investigate the association between socioeconomic position (SEP) throughout the life-course and 451'000 DNA methylation CpG markers across the human genome. We subsequently examine the biological processes in which SEP-related CpGs are involved, and to what extent they correlate with one another.

Methods

Study population

We used data from the SKIPOGH study, a Swiss multicenter population-based study investigating genetic and environmental determinants of health-related outcomes in the Swiss population. Study participants were recruited in the city of Lausanne and the cantons of Geneva and Bern between 2009 and 2013 as previously described [4, 18]. Inclusion criteria were: (1) written informed consent; (2) 18 years of age; (3) Caucasian origin; (5) at least one first-degree family members willing to participate to the study. Women who reported being pregnant were excluded from the study. All included participants attended a morning medical visit after an overnight fast, provided a blood sample, completed a self-administered questionnaire inquiring about life and medical history, and were asked to collect urine over 24 hours. All participants signed a written informed consent.

Life-course socioeconomic position

We examined nine different SEP indicators across the life-course in relation to genome-wide CpG methylation. Father's occupational position, material and financial conditions during infancy, and father and mother's education were used as early-life SEP indicators. SEP indicators in adulthood included participant's education, last known occupational position, monthly household income, and an indicator of financial difficulties inquiring whether the participant would face difficulties paying food, rent, charges, insurance or loans throughout the month. SEP indicators were divided into three categories: high (most favorable – reference group), middle, and low (least favorable) as described in Annex I. Socioeconomic trajectories from childhood to adulthood were generated using father's occupational position and participant's last known occupational position. Five trajectories were possible: stable high (highest-most favorable), upward, stable middle, downward, and stable low trajectory (lowest-least favorable) (Annex I).

CpG DNA methylation measurement and data pre-processing

Genome-wide DNA methylation from peripheral blood mononuclear cells (PBMC) was measured in 256 SKIPOGH participants using the Infinium Human Methylation450 BeadChip microarray of Illumina (HM450), measuring the methylation status of 451'522 CpG sites. For a different set of 451 SKIPOGH participants, genome-wide DNA methylation was measured using the Infinium MethylationEPIC v1.0 microarray (EPIC), assessing the methylation status of 898'918 CpG sites. For both HM450 and EPIC chips, missing values for CpG methylation data were imputed according to the nearest neighbor averaging procedure, followed by a logit transformation of the data [19]. The imputed and transformed CpG methylation data were subsequently denoised for five random effect categorical variables:

Illumina array, array position, plate level, participant's recruitment center, and participant's family index, whereby the residuals of the random effect variables were directly added to the transformed CpG methylation data, enabling the implementation of fixed-effect regression models. Of the 451'000 CpGs present in both chips, data transformation could not be achieved for 29'943 markers due to extensive missing values, yielding 421'057 CpGs in 707 participants available for analyses.

Covariates

The main covariates included in the present analyses were sex (dichotomous), age at blood sampling (continuous), seasonality of blood sampling (categorical), PBMC composition corrected according to Houseman procedure (continuous: CD8T, CD4T, NK, B-cells, Monocytes, Granulocytes), and chip type (categorical, random effect variable: HM450, EPIC) [20]. Additional covariates included self-reported health behaviors, namely smoking status, sedentary behavior, and hazardous alcohol drinking, along with self-reported or diagnosed cardiometabolic disorders, namely obesity, hypertension, diabetes, and history of coronary heart disease (CHD) as described in Annex II.

Statistical analyses

Univariate linear regression

We applied fixed-effect univariate linear regression models for the associations between life-course SEP indicators and differential methylation of genome-wide CpG markers [21]. We used categorized life-course SEP indicators as the main exposure variables (continuous – Lowest versus Highest), and imputed, logit-transformed, and denoised CpG methylation markers as the response variables, adjusting for main covariates (M1: age, sex, seasonality,

PBMC composition, chip type). We further implemented three additional regression models between life-course SEP and CpGs identified in the first model, additionally adjusting for health behaviors (M2), cardiometabolic disorders (M3), and health behaviors *and* cardiometabolic disorders (M4).

Gene ontology enrichment

To examine the biological pathways in which the SEP-related CpGs are involved, we applied the CpG-based gene ontology enrichment approach using the "missMethyl" tool [22]. "missMethyl" uses the "Gene Ontology" (GO) collection which identifies fundamental biological pathways (BP-Biological Process, MF-Molecular Function, CC-Cellular Component), and the "Kyoto Encyclopedia of Genes and Genomes" (KEGG) collection which highlights health outcomes and diseases related to a given set of CpGs [22]. We also used the "PANTHER" gene ontology platform which uses gene names (intragenic CpGs only) to provide potential biological processes and pathways [23].

Network analyses

To investigate for potential inter-correlations between CpGs related to life-course SEP indicators, we implemented a network analysis by applying neighborhood selection and partial correlation methods [24]. We identified the number of clusters (groups of inter-correlated CpGs within the network) by using the Integrated Completed Likelihood criterion (ICL), whereby the number of clusters (Q) is determined by the maximum ICL value [24].

All statistical analyses performed in this study were carried out using the R statistical software and relevant CRAN and Bioconductor packages (R Foundation for Statistical Computing, Vienna, Austria). Statistical significances were set at $p<0.05$, and according to Bonferroni

(N=421’057 CpGs) and Benjamini-Hochberg (BH, p<0.05 - N=421’057 CpGs) thresholds when accounting for multiple testing.

Results

From the initial 707 SKIPOGH participants, we excluded 17 individuals because of missing data for one or more covariates (sex, age, seasonality, PBMC composition, health behaviors, and cardiometabolic disorders). Compared with the included participants, those excluded were more frequently men (76% vs. 47%, p=0.03).

We summarize the main characteristics of the sample stratified by sex in **Table 1**. We observed that men had a higher count of CD8T cells (p<0.001), whereas women had higher NK (p<0.013) and Monocyte counts (p<0.001). More men than women had a high occupational position (30% vs. 13%, p<0.001), a high household income (42% vs. 34%, p=0.051) and experienced more favorable occupational trajectories across the life-course (stable high: 11% vs. 7%, p=0.005). Furthermore, a greater proportion of men were current smokers, had a hazardous alcohol consumption, a higher BMI, and were more affected by hypertension and diabetes when compared to women.

In **Figures 1** and **2**, we show the mean methylation difference (β) and P-value distribution for linear regressions between life-course SEP and CpG markers, adjusting for the main covariates (Manhattan plots – Supplementary Figures 1-2). While early-life SEP indicators were not associated with any of the CpGs (**Figure 1**), household income in adulthood, financial difficulties in adulthood, and occupational trajectories across the life-course were associated with two, 153, and six CpGs, respectively (**Figure 2** - BH significance threshold**;**

Table 2-M1). The two CpGs related to the lowest (least favorable) versus the highest (most favorable) household income were the intragenic ZNF385D-cg17024919 (β=-0.55, p=1.20E-07), and the intergenic cg21900073 (β=-0.55, p=1.75E-07), whereas the top three CpGs related to the least favorable versus the most favorable level of financial difficulties included the intragenic KIAA0319L-cg24940583 (β=-0.47, p=9.78E-09), TRIO-cg21618273 (β=-0.24, p=1.14E-07), KY-cg14313576 (β=-0.27, p=1.22E-07). The top three CpGs associated with the lowest versus the highest occupational trajectories were the intragenic BBS9-cg13362105 (β=-0.61, p=5.52E-08), DSC3-cg11722699 (β=0.43, p=1.34E-07), and KCNQ1-cg14089425 (β=-0.45, p=3.74E-07). Of the 161 SEP-related CpGs, 41 CpGs were intergenic, while 120 CpGs were located within known genes, including 80 CpGs located in the gene body, 24 CpGs in the gene promoter, and 16 CpGs in other intragenic regions. Furthermore, we observed that 156 CpGs were hypomethylated (β<0), whereas five CpGs were hypermethylated (β>0), namely ZBTB16-cg10827488, ARL11-cg01425731, KLKB1-cg05740254, C8orf84-cg17173767, and DSC3-cg11722699.

In Table 2 M2-M4, we show the regression estimates for the associations between SEP indicators and the 161 CpG markers, further adjusting for health behaviors (M2), cardiometabolic disorders (M3), and health behaviors *and* cardiometabolic disorders (M4). The eight CpGs initially associated with household income and occupational trajectories (M1: ZNF385D-cg17024919, cg21900073, BBS9-cg13362105, DSC3-cg11722699, KCNQ1-cg14089425, BTBD11-cg27431274, PIRT-cg06881239, cg06803821) remained significantly and consistently associated with these indicators across the three additionally adjusted regression models (M2-M4). Of the 153 CpGs initially associated with financial difficulties (M1), 90 markers were no longer associated with this indicator upon adjusting for health behaviors (M2), 109 CpGs upon adjusting for cardiometabolic disorders (M3), and 128 CpGs

were no longer related to financial difficulties upon accounting for health behaviors *and* cardiometabolic disorders (M4).

In **Table 3**, we present the top 30 GO and KEGG biological pathways identified according to the 161 SEP-related CpGs (Table 2). The GO algorithm identified 326 significant pathways and structures involved in various processes, most of which were related to cell signaling and communication (ankyrin binding, plasma membrane, signal transduction, receptor clustering, ion channel binding), as well as metabolic and physiological processes (cardiac cell polarization and potential, muscle contraction, blood metabolism). Alternatively, the KEGG algorithm identified seven significant pathways, out of which five were related to immune and oncogenic processes (pathways in cancer, primary immunodeficiency, choline metabolism in cancer, intestinal immune network for IgA production, Rap1 signaling pathway), involving intragenic CpGs located within the immune-related CCR3, ITGAL, CCL22, PRKCB, TNFRSF13B, RUNX3, SIT1, KALRN, TIGIT, NOTCH4, TSPAN4, RPL23A, and TRIO genes, and intragenic CpGs within the cancer-related ALK, EPHB2, NOTCH4, PRKCB, FGF1, ADSSL1, miR-134, RBP1, RPL23A, GLI2, and TP53I11 genes (Table 2) [22, 23].

In **Figure 3**, we show a network of SEP-related CpG markers. Of the 161 CpGs initially identified in the linear regression model (Table 2-M1), 91 CpGs were related to at least one other CpG and used to build the network. Using the ICL criterion (Supplementary Figure 3), we identified two CpG clusters; the first cluster including 62 CpGs (red), out of which 60 CpGs were associated with financial difficulties, whereas the two other CpGs were related to household income and occupational trajectories, respectively; and the second cluster including 29 CpGs (yellow) associated with financial difficulties. While the first cluster presented a

more diffuse structure with the intergenic cg27109056 and the intragenic RBP1-cg16171849 as the most central CpGs, the second cluster was much more compact and displayed stronger inter-correlations (Supplementary Figure 4), with C22orf39-cg06501716, RPL23A-cg15036326, PRKCB-cg09327847, and miR134-cg10734581 as the most central CpGs.

Sensitivity analyses

Using Fisher's exact tests for count data, we further explored whether there were associations between the identified network clusters, CpG methylation status (hyper/hypomethylation), CpG location (detailed intragenic position; intragenic/intergenic), and SEP indicators (financial difficulties, household income, occupational trajectories), but found no meaningful relations between these factors (Supplementary Tables 1-9).

Discussion

In this Swiss population-based study, we found that financial difficulties in adulthood, low household income, and adverse socioeconomic trajectories across the life-course are associated with the differential methylation of a large number of genome-wide CpG markers, with 97% of the identified CpGs being hypomethylated. Furthermore, we observed that after adjusting for health behaviors and cardiometabolic disorders, a substantial number of CpGs were no longer associated with SEP indicators, suggesting that these CpG markers may potentially mediate the effect of SEP on these cardiometabolic conditions. Finally, we found that the identified CpGs were strongly related to cell signaling, immune, and cancer-related processes, and tended to cluster into two main groups.

While we failed to retrieve any of the SEP-related CpGs identified in former studies, we found common biological processes and pathways between our study and previous investigations [5, 6, 25, 26]. Among the significantly associated intragenic CpGs, there were multiple genes involved in inflammatory and immune processes, including CCR3, ITGAL, CCL22, PRKCB, TNFRSF13B, RUNX3, SIT1, KALRN, TIGIT, NOTCH4, TSPAN4, RPL23A, and TRIO genes, which is consistent with previous research reporting a strong association between life-course SEP or dominance rank, and a differential methylation of CpGs located within pro-inflammatory genes [5, 6, 23, 26]. From the pathophysiological perspective, our results tend to be in line with former findings, as adverse socioeconomic circumstances have been strongly associated with aberrant inflammation, eventually leading to the occurrence of chronic diseases such as atherosclerosis, diabetes, and cancer [7, 27-29]. We also identified several intragenic CpGs located within cancer-related genes, including the two highly interconnected RBP1-cg1617849 (network-cluster 1) and RPL23A-cg15036326 (network-cluster 2), which is consistent with previous research suggesting that adverse socioeconomic circumstances may lead to a higher cancer risk, with DNA methylation as a potential underlying mechanism for this association [14, 30-34]. Furthermore, we observed that the great majority of the SEP-related CpG markers were hypomethylated, which is consistent with most previous research reporting overall hypomethylation in response to adverse socioeconomic circumstances [5, 6, 32, 35]. We also observed that upon accounting for health behaviors and/or cardiometabolic disorders, a substantial number of CpGs were no longer associated with SEP indicators, which is explained by variations in health behaviors and cardiometabolic disorders, and may suggest a potential mediating effect between SEP, health behaviors, DNA methylation, and cardiometabolic disorders [36]. In particular, we found that smoking, obesity, CHD, and diabetes were significantly associated with 29 of the 128 “dropped” CpG markers in the fully adjusted model (results available on request).

Finally, unlike previous research reporting an association between early-life socioeconomic circumstances and a differential CpG methylation in multiple gene promoters, we did not observe any associations involving SEP in childhood [17]. These results may be attributed to a lack of statistical power, or to a retrospective self-reporting of childhood SEP in our study [37], whereas former research reporting a significant relation between early-life socioeconomic circumstances and differential CpG methylation was conducted in a birth cohort with a more extensive measurement of SEP across different life periods [17].

Strengths and limitations

Our study has several strengths, the first being the untargeted approach using 451'000 CpG markers across the entire human genome. Second, we investigated the role of nine different SEP indicators in childhood and adulthood, which allowed us to explore SEP-driven methylation changes across different life phases.

Our study also has some limitations to acknowledge. First, the relatively small sample size may lead to a limited statistical power, which restricts the ability to detect small effect-size associations. Second, unlike specific exposures producing strong and consistent DNA methylation changes in most populations (i.e. cigarette smoking), we found generally weak associations, with only three CpGs being associated with SEP indicators at Bonferroni threshold. Third, except for the CpG located within the ZNF385 gene (DNA binding) whose expression was modified as a result of SEP [25], we failed to retrieve any of the previously SEP-related methylation or transcription markers. Fourth, the relation between SEP-related CpG markers and gene expression shall also be investigated in order to determine how the differential methylation of CpGs affects the actual phenotype, eventually translating into a higher disease risk. This "multi-omics" approach, combining epigenomics and transcriptomics will thoroughly explore the correlations between the SEP-related CpGs, transcriptome-wide

RNAs, as well as blood inflammation markers (C-reactive protein, cytokines), and will be the object of our next research. Moreover, we must interpret the suggested relation between CpG methylation and inflammatory and oncogenic pathways cautiously, as it is impossible to determine which process occurred in the first place due to the overall cross-sectional nature of the present study. Finally, the use of peripheral blood mononuclear cells for assessing DNA methylation represents an additional issue due to heterogeneity in leukocyte composition, individual and population-based differences, and an important cell-turnover, which may eventually confound DNA methylation assessment [38]. However, we applied the Houseman procedure to account for these factors [20].

Conclusion

In summary, our findings suggest that adverse socioeconomic circumstances lead to a differential methylation of inflammation and cancer-related CpG markers in the human epigenome. However, the relation between socioeconomic factors and identified CpGs shall also be investigated in other populations to provide additional validity to our findings. Furthermore, future investigations shall explore the actual relation between identified CpG markers and inflammation and cancer-related outcomes. Finally, a longitudinal approach shall also be implemented in order to disentangle the causal pathway involving adverse socioeconomic circumstances, DNA methylation, inflammation, and disease occurrence.

Table 1: General characteristics of included participants by sex

	Men (N=329)	Women (N=361)	P-value [a,b]
Age (μ±SD, y)	52.4 (±15.8)	52.5 (±15.3)	0.948
Recruitement center (random effect variable)			
Lausanne	137 (42%)	167 (46%)	0.474
Geneva	142 (43%)	144 (40%)	
Bern	50 (15%)	50 (14%)	
Seasonality of recruitement			
Spring	104 (32%)	107 (30%)	0.89
Summer	70 (22%)	75 (21%)	
Fall	74 (23%)	84 (24%)	
Winter	74 (23%)	84 (24%)	
PBMC composition			
CD8T (μ±SD)	4.6e-02 (±4.1e-02)	6.5e-02 (±4.2e-02)	<0.001
CD4T (μ±SD)	1.8e-01 (±5.9e-02)	1.8e-01 (±6.7e-02)	0.411
NK (μ±SD)	6.1e-02 (±3.7e-02)	5.4e-02 (±3.7e-02)	0.013
Bcells (μ±SD)	4.3e-02 (±3.0e-02)	4.2e-02 (±4.4e-02)	0.361
Monocytes (μ±SD)	8.2e-02 (±2.4e-02)	7.3e-02 (±2.5e-02)	<0.001
Granulocyte (μ±SD)	6.0e-01 (±9.8e-02)	5.9e-01 (±1.0e-01)	0.298
Illumina chip			
HM450	107 (33%)	129 (36%)	0.551
EPIC	215 (67%)	227 (64%)	
Early-life SEP			
Father's occupational position			
High	75 (23%)	90 (25%)	0.801
Middle	127 (40%)	132 (37%)	
Low	119 (37%)	131 (37%)	
Infancy conditions			
High	94 (29%)	88 (25%)	0.413
Middle	164 (51%)	198 (56%)	
Low	64 (20%)	70 (20%)	
Father's education			
High	80 (25%)	92 (26%)	0.907
Middle	130 (41%)	136 (39%)	
Low	110 (34%)	123 (35%)	
Mother's education			
High	41 (13%)	46 (13%)	0.862
Middle	111 (35%)	128 (37%)	
Low	166 (52%)	175 (50%)	
Adult SEP			
Participant's education			
High	132 (41%)	134 (38%)	0.121
Middle	146 (45%)	150 (42%)	
Low	44 (14%)	72 (20%)	
Occupational position			
High	93 (30%)	42 (13%)	<0.001
Middle	73 (24%)	137 (42%)	
Low	143 (46%)	145 (45%)	
Household income			
High	119 (42%)	104 (34%)	0.051
Middle	121 (43%)	132 (43%)	
Low	43 (15%)	69 (23%)	
Financial difficulties 1 [c]			
No difficulties	213 (67%)	235 (67%)	0.91
Average difficulties	69 (22%)	77 (22%)	
Important difficulties	38 (12%)	38 (11%)	
Life-course occupational trajectories			
Stable high	33 (11%)	22 (7%)	0.005
Upward	88 (29%)	63 (20%)	
Stable mid.	31 (10%)	55 (17%)	
Downward	93 (30%)	111 (35%)	
Stable low	63 (20%)	70 (22%)	
Health behaviors			
Current smoking (N,%)	96 (30%)	74 (21%)	0.014
Hazardous alcohol intake (N,%) [e]	36 (11%)	0 (0%)	<0.001

Sedentary behavior (N,%)	130 (40%)	145 (41%)	1
CMD			
BMI (μ±SD,kg/m2)	26.6 (±4.1)	24.8 (±4.8)	<0.001
Obesity (N,%)	54 (17%)	48 (13%)	0.208
Hypertension (N,%)	108 (34%)	77 (22%)	<0.001
Diabetes (N,%)	25 (8%)	13 (4%)	0.023
CHD (N,%)	10 (3%)	5 (1%)	0.095

CHD, coronary heart disease; PBMS, peripheral blood mononuclear cell; SEP, socioeconomic position
Data are mean ± SD for continuous variables and n (%) for categorical variables
[a] The Mann-Whitney U-test was performed between men and women for continuous variables.
[b] The $\chi 2$ contingency test was performed between men and women for categorical variables
[c] The definition of health behaviors and cardiometabolic disorders is given in Annex II

Table 2: Summary of CpG markers (N=161) significantly associated with life-course SEP variables at Benjamini-Hochberg (BH) significance threshold in the model adjusted for main covariates (M1), and the models additionally adjusted for health behaviors and/or cardiometabolic disorders (M2-M4)

		M1 [a]			M2:M1 + HB [b]			M3:M1 + CMD [c]			M4:M1 + HB + CMD [d]					
CpG	**SEP**	**Beta**	**SE**	**P-value**	**Beta**	**SE**	**P-value [e]**	**Beta**	**SE**	**P-value [e]**	**Beta**	**SE**	**P-value [e]**	**Gene**	**Location [f]**	**Chromosome**
cg17024919	Household income	-0.55	0.10	1.20E-07	-0.50	0.10	**1.26E-06**	-0.54	0.10	**1.78E-07**	-0.50	0.10	**1.78E-06**	ZNF385D	Body	chr3
cg21900073	Household income	-0.41	0.08	1.75E-07	-0.41	0.08	**2.47E-07**	-0.39	0.08	**4.27E-07**	-0.39	0.08	**6.31E-07**		Intergenic	chr4
cg24940583	Financial difficulties	-0.47	0.08	9.78E-09	-0.46	0.08	**3.53E-08**	-0.49	0.08	**6.61E-09**	-0.47	0.08	**3.27E-08**	KIAA0319L	5'UTR	chr1
cg21618273	Financial difficulties	-0.24	0.05	1.14E-07	-0.24	0.05	**3.21E-07**	-0.25	0.05	**1.03E-07**	-0.24	0.05	**3.11E-07**	TRIO	Body	chr5
cg14313576	Financial difficulties	-0.27	0.05	1.22E-07	-0.27	0.05	**2.40E-07**	-0.27	0.05	**3.40E-07**	-0.26	0.05	**7.02E-07**	KY	Body	chr3
cg20171011	Financial difficulties	-0.36	0.07	1.72E-07	-0.35	0.07	**4.13E-07**	-0.36	0.07	**2.23E-07**	-0.35	0.07	**5.81E-07**	TSPAN4	Body	chr11
cg10576132	Financial difficulties	-0.29	0.06	3.28E-07	-0.28	0.06	**1.20E-06**	-0.28	0.06	**1.17E-06**	-0.27	0.06	**3.70E-06**	TXNDC3	Body	chr7
cg05946118	Financial difficulties	-0.28	0.05	3.47E-07	-0.28	0.05	**4.62E-07**	-0.28	0.05	**3.44E-07**	-0.28	0.06	**5.25E-07**		Intergenic	chr16
cg13361798	Financial difficulties	-0.54	0.11	4.76E-07	-0.56	0.11	**2.29E-07**	-0.52	0.11	**1.19E-06**	-0.54	0.11	**6.16E-07**		Intergenic	chr22
cg07565228	Financial difficulties	-0.39	0.08	5.58E-07	-0.40	0.08	**5.65E-07**	-0.39	0.08	**8.31E-07**	-0.39	0.08	**1.04E-06**	LDHD	Body	chr16
cg17007693	Financial difficulties	-0.31	0.06	7.94E-07	-0.29	0.06	**3.94E-06**	-0.30	0.06	**2.10E-06**	-0.28	0.06	1.09E-05		Intergenic	chr18
cg14531564	Financial difficulties	-0.33	0.07	9.14E-07	-0.31	0.07	**2.80E-06**	-0.32	0.07	**1.92E-06**	-0.30	0.07	7.18E-06	SDF4	Body	chr1
cg11195733	Financial difficulties	-0.44	0.09	1.14E-06	-0.49	0.09	**1.15E-07**	-0.46	0.09	**6.42E-07**	-0.51	0.09	**5.26E-08**	TECPR2	Body	chr14
cg05259836	Financial difficulties	-0.46	0.09	1.15E-06	-0.46	0.09	**1.40E-06**	-0.45	0.09	**2.37E-06**	-0.45	0.10	**2.95E-06**		Intergenic	chr6
cg09251508	Financial difficulties	-0.35	0.07	1.18E-06	-0.35	0.07	**1.27E-06**	-0.32	0.07	8.55E-06	-0.32	0.07	8.54E-06		Intergenic	chr3
cg11875995	Financial difficulties	-0.37	0.08	1.59E-06	-0.37	0.08	**2.61E-06**	-0.37	0.08	**2.37E-06**	-0.37	0.08	4.73E-06		Intergenic	chr8
cg25430442	Financial difficulties	-0.45	0.09	1.65E-06	-0.47	0.09	**4.87E-07**	-0.43	0.09	**5.97E-06**	-0.45	0.09	**2.08E-06**		Intergenic	chr2
cg27054610	Financial difficulties	-0.39	0.08	1.66E-06	-0.38	0.08	**3.23E-06**	-0.39	0.08	**1.49E-06**	-0.38	0.08	**3.23E-06**	NOTCH4	Body	chr6
cg05398769	Financial difficulties	-0.43	0.09	1.67E-06	-0.43	0.09	**2.75E-06**	-0.42	0.09	**4.14E-06**	-0.41	0.09	7.96E-06	CASZ1	5'UTR	chr1
cg10827488	Financial difficulties	0.25	0.05	1.68E-06	0.24	0.05	**7.53E-06**	0.25	0.05	**3.18E-06**	0.23	0.05	1.49E-05	ZBTB16	Body	chr11
cg24069724	Financial difficulties	-0.47	0.10	1.77E-06	-0.50	0.10	**4.29E-07**	-0.50	0.10	**6.95E-07**	-0.53	0.10	**1.98E-07**	GLI2	Body	chr2
cg19654061	Financial difficulties	-0.48	0.10	1.79E-06	-0.46	0.10	**4.65E-06**	-0.46	0.10	5.96E-06	-0.44	0.10	1.78E-05	ALPP	1stExon	chr2
cg22012299	Financial difficulties	-0.34	0.07	1.97E-06	-0.33	0.07	**2.81E-06**	-0.32	0.07	1.02E-05	-0.31	0.07	1.70E-05	ITGBL1	Body	chr13
cg10588834	Financial difficulties	-0.44	0.09	1.98E-06	-0.44	0.09	**2.01E-06**	-0.45	0.09	**1.86E-06**	-0.45	0.09	**2.27E-06**	AUTS2	Body	chr7
cg01425731	Financial difficulties	0.34	0.07	2.01E-06	0.31	0.07	1.75E-05	0.34	0.07	**3.00E-06**	0.31	0.07	2.41E-05	ARL11	5'UTR	chr13
cg26148774	Financial difficulties	-0.33	0.07	2.22E-06	-0.32	0.07	**4.30E-06**	-0.35	0.07	**8.31E-07**	-0.34	0.07	**1.90E-06**	OR10P1	TSS1500	chr12
cg05229416	Financial difficulties	-0.30	0.06	2.53E-06	-0.29	0.06	**6.14E-06**	-0.29	0.06	8.38E-06	-0.28	0.07	2.06E-05	EPHB2	Body	chr1
cg06332621	Financial difficulties	-0.26	0.05	2.73E-06	-0.25	0.05	**3.88E-06**	-0.26	0.05	**2.68E-06**	-0.26	0.06	4.12E-06	RBM47	TSS1500	chr4
cg20948431	Financial difficulties	-0.33	0.07	2.74E-06	-0.30	0.07	1.53E-05	-0.34	0.07	**1.22E-06**	-0.32	0.07	7.05E-06	C4orf10	Body	chr4
cg01527394	Financial difficulties	-0.47	0.10	2.79E-06	-0.47	0.10	**3.23E-06**	-0.46	0.10	6.98E-06	-0.46	0.10	8.39E-06	TBC1D22A	Body	chr22
cg18796704	Financial difficulties	-0.49	0.10	2.80E-06	-0.52	0.10	**1.03E-06**	-0.45	0.10	2.27E-05	-0.47	0.11	1.02E-05	ENPP1	3'UTR	chr6
cg00052588	Financial difficulties	-0.44	0.09	3.06E-06	-0.43	0.09	**4.95E-06**	-0.44	0.09	**3.39E-06**	-0.43	0.09	5.68E-06		Intergenic	chr16
cg26197254	Financial difficulties	-0.23	0.05	3.12E-06	-0.22	0.05	**6.92E-06**	-0.21	0.05	1.68E-05	-0.21	0.05	4.50E-05	FLJ37543	Body	chr5
cg19984355	Financial difficulties	-0.33	0.07	3.15E-06	-0.33	0.07	**5.06E-06**	-0.31	0.07	1.67E-05	-0.30	0.07	3.10E-05		Intergenic	chr5
cg24180759	Financial difficulties	-0.23	0.05	3.18E-06	-0.23	0.05	**5.11E-06**	-0.22	0.05	7.59E-06	-0.22	0.05	1.18E-05	ODZ2	Body	chr5
cg07617814	Financial difficulties	-0.29	0.06	3.21E-06	-0.28	0.06	**6.19E-06**	-0.27	0.06	1.50E-05	-0.26	0.06	3.25E-05	ZNF217	1stExon	chr20
cg17034360	Financial difficulties	-0.50	0.11	3.21E-06	-0.48	0.11	**6.30E-06**	-0.50	0.11	**3.90E-06**	-0.48	0.11	1.03E-05	GPR177	Body	chr1
cg03377767	Financial difficulties	-0.25	0.05	3.26E-06	-0.24	0.05	1.13E-05	-0.25	0.05	**3.75E-06**	-0.24	0.06	1.26E-05	MSGN1	TSS1500	chr2
cg20488756	Financial difficulties	-0.49	0.10	3.29E-06	-0.48	0.11	**6.68E-06**	-0.51	0.11	**2.07E-06**	-0.50	0.11	4.24E-06	TRIM15	1stExon	chr6
cg19043851	Financial difficulties	-0.36	0.08	3.44E-06	-0.37	0.08	**3.07E-06**	-0.35	0.08	1.03E-05	-0.36	0.08	7.66E-06		Intergenic	chr10

cg21733502	Financial difficulties	-0.47	0.10	3.44E-06	-0.47	0.10	**4.95E-06**	-0.44	0.10	1.80E-05	-0.44	0.10	2.64E-05	ZSCAN5B	Body	chr19
cg00293599	Financial difficulties	-0.43	0.09	3.52E-06	-0.45	0.09	**1.51E-06**	-0.46	0.09	**1.48E-06**	-0.48	0.09	**5.66E-07**	SPDEF	3'UTR	chr6
cg16431352	Financial difficulties	-0.29	0.06	3.75E-06	-0.28	0.06	8.76E-06	-0.27	0.06	2.00E-05	-0.26	0.06	5.28E-05		Intergenic	chr2
cg08816023	Financial difficulties	-0.34	0.07	3.84E-06	-0.34	0.07	**5.45E-06**	-0.32	0.07	2.07E-05	-0.32	0.08	2.97E-05	FGF1	5'UTR	chr5
cg15805567	Financial difficulties	-0.28	0.06	3.90E-06	-0.28	0.06	**3.04E-06**	-0.27	0.06	9.88E-06	-0.27	0.06	8.25E-06	ARHGAP22	Body	chr10
cg26405835	Financial difficulties	-0.50	0.11	3.94E-06	-0.51	0.11	**3.18E-06**	-0.53	0.11	**1.46E-06**	-0.54	0.11	**1.01E-06**	NCRNA00160	TSS1500	chr21
cg12252328	Financial difficulties	-0.42	0.09	4.00E-06	-0.41	0.09	**7.68E-06**	-0.41	0.09	9.24E-06	-0.40	0.09	1.98E-05	ALK	Body	chr2
cg04716530	Financial difficulties	-0.23	0.05	4.06E-06	-0.21	0.05	5.10E-05	-0.22	0.05	1.19E-05	-0.19	0.05	1.61E-04	ITGAL	Body	chr16
cg00045118	Financial difficulties	-0.27	0.06	4.15E-06	-0.27	0.06	8.87E-06	-0.26	0.06	1.37E-05	-0.25	0.06	3.18E-05	RUNX1T1	Body	chr8
cg14883070	Financial difficulties	-0.46	0.10	4.16E-06	-0.50	0.10	**8.78E-07**	-0.46	0.10	**6.65E-06**	-0.49	0.10	**2.00E-06**	SPIRE1	5'UTR	chr18
cg19928195	Financial difficulties	-0.26	0.06	4.25E-06	-0.27	0.06	**4.51E-06**	-0.24	0.06	3.37E-05	-0.24	0.06	3.67E-05	KALRN	TSS1500	chr3
cg02854972	Financial difficulties	-0.26	0.06	4.35E-06	-0.26	0.06	**6.74E-06**	-0.25	0.06	1.62E-05	-0.24	0.06	2.54E-05		Intergenic	chr4
cg06519434	Financial difficulties	-0.23	0.05	4.47E-06	-0.23	0.05	9.91E-06	-0.23	0.05	1.10E-05	-0.22	0.05	2.78E-05	SCN5A	Body	chr3
cg10734581	Financial difficulties	-0.24	0.05	4.49E-06	-0.25	0.05	**3.87E-06**	-0.23	0.05	1.62E-05	-0.24	0.05	1.53E-05	MIR134	TSS1500	chr14
cg27488095	Financial difficulties	-0.29	0.06	4.95E-06	-0.28	0.06	1.17E-05	-0.29	0.06	**4.31E-06**	-0.28	0.06	1.12E-05	TM4SF5	1stExon	chr17
cg08745960	Financial difficulties	-0.45	0.10	5.04E-06	-0.48	0.10	**1.32E-06**	-0.44	0.10	**1.10E-05**	-0.47	0.10	**2.76E-06**		Intergenic	chr22
cg00442174	Financial difficulties	-0.49	0.11	5.15E-06	-0.47	0.11	1.50E-05	-0.49	0.11	9.68E-06	-0.46	0.11	2.86E-05	PIGL	Body	chr17
cg01940273	Financial difficulties	-0.47	0.10	5.36E-06	-0.27	0.09	3.13E-03	-0.46	0.10	8.21E-06	-0.25	0.09	5.92E-03		Intergenic	chr2
cg22526555	Financial difficulties	-0.40	0.09	5.49E-06	-0.40	0.09	**6.26E-06**	-0.42	0.09	**1.95E-06**	-0.43	0.09	**2.20E-06**	DSCR10	Body	chr21
cg09364677	Financial difficulties	-0.49	0.11	5.49E-06	-0.49	0.11	**7.50E-06**	-0.52	0.11	**2.07E-06**	-0.52	0.11	**3.10E-06**		Intergenic	chr16
cg09091373	Financial difficulties	-0.47	0.10	5.65E-06	-0.47	0.10	**7.31E-06**	-0.47	0.10	**4.85E-06**	-0.47	0.10	6.35E-06	TP53I11	Body	chr11
cg10221172	Financial difficulties	-0.31	0.07	5.89E-06	-0.31	0.07	**3.91E-06**	-0.27	0.07	6.73E-05	-0.28	0.07	4.58E-05	SASH1	Body	chr6
cg15518883	Financial difficulties	-0.15	0.03	5.96E-06	-0.15	0.03	**2.79E-06**	-0.15	0.03	**3.85E-06**	-0.16	0.03	**1.61E-06**	SIT1	Body	chr9
cg21723559	Financial difficulties	-0.32	0.07	5.97E-06	-0.29	0.07	3.59E-05	-0.32	0.07	8.31E-06	-0.29	0.07	5.09E-05	PIGT	Body	chr20
cg13820281	Financial difficulties	-0.38	0.08	6.07E-06	-0.39	0.08	**4.23E-06**	-0.37	0.09	1.49E-05	-0.38	0.09	1.36E-05		Intergenic	chr9
cg05209330	Financial difficulties	-0.28	0.06	6.12E-06	-0.28	0.06	9.70E-06	-0.27	0.06	1.90E-05	-0.27	0.06	2.68E-05	P4HA2	Body	chr5
cg11904429	Financial difficulties	-0.26	0.06	6.17E-06	-0.26	0.06	**6.59E-06**	-0.26	0.06	9.59E-06	-0.26	0.06	9.40E-06	CD70	TSS1500	chr19
cg16519923	Financial difficulties	-0.22	0.05	6.49E-06	-0.19	0.05	8.99E-05	-0.21	0.05	3.50E-05	-0.18	0.05	4.70E-04	ITGAL	Body	chr16
cg08536617	Financial difficulties	-0.29	0.06	6.55E-06	-0.27	0.06	2.17E-05	-0.27	0.06	2.02E-05	-0.26	0.06	6.69E-05		Intergenic	chr10
cg26034811	Financial difficulties	-0.29	0.06	6.72E-06	-0.28	0.06	1.65E-05	-0.28	0.06	1.18E-05	-0.27	0.06	3.22E-05	ADSSL1	Body	chr14
cg12660445	Financial difficulties	-0.31	0.07	6.83E-06	-0.29	0.07	2.32E-05	-0.30	0.07	1.94E-05	-0.28	0.07	7.07E-05	SNORD18A	TSS200	chr15
cg07568203	Financial difficulties	-0.36	0.08	7.09E-06	-0.35	0.08	1.48E-05	-0.33	0.08	3.08E-05	-0.33	0.08	6.18E-05	OR51B5	TSS1500	chr11
cg16006965	Financial difficulties	-0.45	0.10	7.23E-06	-0.40	0.10	5.99E-05	-0.43	0.10	2.29E-05	-0.38	0.10	2.10E-04	GCET2	TSS1500	chr3
cg18247852	Financial difficulties	-0.41	0.09	7.53E-06	-0.43	0.09	**2.57E-06**	-0.42	0.09	**5.78E-06**	-0.44	0.09	**2.23E-06**	SLC16A3	Body	chr17
cg18461347	Financial difficulties	-0.28	0.06	7.57E-06	-0.28	0.06	9.30E-06	-0.26	0.06	5.20E-05	-0.26	0.06	5.98E-05	MAGI2	Body	chr7
cg27639142	Financial difficulties	-0.30	0.07	7.58E-06	-0.31	0.07	**8.25E-06**	-0.28	0.07	5.41E-05	-0.27	0.07	7.53E-05	KLF15	5'UTR	chr3
cg16391678	Financial difficulties	-0.23	0.05	7.65E-06	-0.20	0.05	8.48E-05	-0.22	0.05	2.78E-05	-0.19	0.05	3.19E-04	ITGAL	Body	chr16
cg05740254	Financial difficulties	0.48	0.11	7.88E-06	0.44	0.11	3.39E-05	0.49	0.11	**4.63E-06**	0.46	0.11	2.19E-05	KLKB1	TSS200	chr4
cg26869501	Financial difficulties	-0.33	0.07	7.93E-06	-0.31	0.07	1.90E-05	-0.32	0.07	1.43E-05	-0.31	0.07	4.25E-05	TMPO	Body	chr12
cg22374742	Financial difficulties	-0.28	0.06	8.09E-06	-0.27	0.06	1.69E-05	-0.28	0.06	1.20E-05	-0.27	0.06	2.38E-05	UXS1	Body	chr2
cg02762561	Financial difficulties	-0.41	0.09	8.23E-06	-0.44	0.09	**2.49E-06**	-0.39	0.09	2.78E-05	-0.42	0.09	7.81E-06	PAXIP1	Body	chr7
cg01731783	Financial difficulties	-0.24	0.05	8.35E-06	-0.21	0.05	1.33E-04	-0.22	0.05	6.39E-05	-0.18	0.05	1.01E-03	C14orf43	5'UTR	chr14
cg09246203	Financial difficulties	-0.35	0.08	8.40E-06	-0.32	0.08	4.24E-05	-0.36	0.08	**5.41E-06**	-0.33	0.08	2.91E-05	TIGIT	Body	chr3
cg01693305	Financial difficulties	-0.31	0.07	8.66E-06	-0.30	0.07	2.38E-05	-0.29	0.07	4.00E-05	-0.28	0.07	9.64E-05	CAPZB	TSS1500	chr1
cg16086570	Financial difficulties	-0.24	0.05	8.83E-06	-0.24	0.05	1.19E-05	-0.23	0.05	3.75E-05	-0.22	0.05	5.02E-05		Intergenic	chr5
cg21283739	Financial difficulties	-0.41	0.09	8.96E-06	-0.44	0.09	**1.52E-06**	-0.40	0.09	**1.38E-05**	-0.44	0.09	**2.42E-06**		Intergenic	chr17

cg16455376	Financial difficulties	-0.28	0.06	8.97E-06	-0.27	0.06	1.79E-05	-0.29	0.06	8.50E-06	-0.28	0.06	1.47E-05		Intergenic	chr16
cg09875213	Financial difficulties	-0.22	0.05	9.13E-06	-0.22	0.05	2.18E-05	-0.22	0.05	1.40E-05	-0.22	0.05	3.39E-05	TIFAB	5'UTR	chr5
cg12621745	Financial difficulties	-0.33	0.07	9.22E-06	-0.31	0.08	4.96E-05	-0.34	0.08	9.28E-06	-0.31	0.08	5.71E-05	PLEC1	Body	chr8
cg17174275	Financial difficulties	-0.32	0.07	9.32E-06	-0.29	0.07	6.53E-05	-0.31	0.07	1.65E-05	-0.28	0.07	1.04E-04	ATP10A	TSS1500	chr15
cg24315209	Financial difficulties	-0.23	0.05	9.36E-06	-0.23	0.05	1.53E-05	-0.22	0.05	2.27E-05	-0.22	0.05	3.57E-05	CDK18	Body	chr1
cg01502320	Financial difficulties	-0.24	0.05	9.38E-06	-0.24	0.05	**7.18E-06**	-0.23	0.05	2.41E-05	-0.23	0.05	1.85E-05	TNFRSF13B	TSS200	chr17
cg21949830	Financial difficulties	-0.34	0.08	9.50E-06	-0.31	0.08	5.79E-05	-0.36	0.08	**3.65E-06**	-0.33	0.08	2.51E-05	SLC43A2	Body	chr17
cg13466546	Financial difficulties	-0.36	0.08	9.62E-06	-0.36	0.08	1.03E-05	-0.32	0.08	7.78E-05	-0.32	0.08	1.01E-04	TBC1D16	Body	chr17
cg20747462	Financial difficulties	-0.38	0.09	9.67E-06	-0.37	0.09	2.13E-05	-0.42	0.09	**1.52E-06**	-0.41	0.09	**3.79E-06**	RAMP3	Body	chr7
cg20402658	Financial difficulties	-0.45	0.10	9.75E-06	-0.48	0.10	**2.17E-06**	-0.43	0.10	2.31E-05	-0.47	0.10	5.69E-06	NCALD	Body	chr8
cg23719877	Financial difficulties	-0.32	0.07	9.82E-06	-0.32	0.07	1.55E-05	-0.30	0.07	4.51E-05	-0.30	0.07	7.39E-05	FLNC	Body	chr7
cg15036326	Financial difficulties	-0.24	0.05	9.96E-06	-0.22	0.05	4.21E-05	-0.22	0.05	3.99E-05	-0.21	0.05	1.64E-04	RPL23A	Body	chr17
cg14211837	Financial difficulties	-0.29	0.07	1.01E-05	-0.29	0.07	2.27E-05	-0.28	0.07	2.94E-05	-0.28	0.07	5.93E-05		Intergenic	chr18
cg22573118	Financial difficulties	-0.38	0.09	1.02E-05	-0.37	0.09	1.82E-05	-0.39	0.09	8.12E-06	-0.38	0.09	1.74E-05	CCR3	TSS1500	chr3
cg11345703	Financial difficulties	-0.40	0.09	1.03E-05	-0.40	0.09	1.43E-05	-0.38	0.09	1.53E-05	-0.38	0.09	2.47E-05	SYT7	Body	chr11
cg22478317	Financial difficulties	-0.23	0.05	1.03E-05	-0.21	0.05	6.49E-05	-0.22	0.05	1.76E-05	-0.20	0.05	1.13E-04		Intergenic	chr2
cg11952604	Financial difficulties	-0.48	0.11	1.06E-05	-0.46	0.11	2.92E-05	-0.48	0.11	1.19E-05	-0.45	0.11	4.04E-05	ANP32A	TSS200	chr15
cg03797139	Financial difficulties	-0.42	0.09	1.08E-05	-0.40	0.09	2.83E-05	-0.40	0.09	2.44E-05	-0.39	0.10	6.45E-05	HECA	Body	chr6
cg03724006	Financial difficulties	-0.48	0.11	1.09E-05	-0.50	0.11	**6.86E-06**	-0.48	0.11	1.44E-05	-0.50	0.11	9.76E-06		Intergenic	chr11
cg14166701	Financial difficulties	-0.46	0.10	1.09E-05	-0.44	0.11	3.90E-05	-0.49	0.11	**5.49E-06**	-0.45	0.11	2.91E-05	ASPG	Body	chr14
cg27627493	Financial difficulties	-0.25	0.06	1.10E-05	-0.26	0.06	**3.46E-06**	-0.25	0.06	1.70E-05	-0.26	0.06	5.02E-06		Intergenic	chr15
cg09920804	Financial difficulties	-0.23	0.05	1.10E-05	-0.21	0.05	6.19E-05	-0.23	0.05	1.85E-05	-0.21	0.05	9.99E-05	PLAT	5'UTR	chr8
cg01158415	Financial difficulties	-0.46	0.10	1.13E-05	-0.47	0.11	9.77E-06	-0.44	0.11	4.09E-05	-0.44	0.11	4.88E-05		Intergenic	chr2
cg11786338	Financial difficulties	-0.22	0.05	1.13E-05	-0.21	0.05	4.41E-05	-0.22	0.05	2.78E-05	-0.20	0.05	1.07E-04	SEC11C	Body	chr18
cg24630195	Financial difficulties	-0.43	0.10	1.13E-05	-0.45	0.10	**5.84E-06**	-0.42	0.10	1.91E-05	-0.44	0.10	1.03E-05	IRX2	Body	chr5
cg14906909	Financial difficulties	-0.40	0.09	1.17E-05	-0.40	0.09	1.47E-05	-0.35	0.09	1.38E-04	-0.35	0.09	1.57E-04	ACSS3	Body	chr12
cg16171849	Financial difficulties	-0.34	0.08	1.18E-05	-0.35	0.08	1.07E-05	-0.34	0.08	2.05E-05	-0.34	0.08	1.89E-05	RBP1	Body	chr3
cg09327847	Financial difficulties	-0.23	0.05	1.18E-05	-0.22	0.05	3.79E-05	-0.23	0.05	1.82E-05	-0.22	0.05	6.07E-05	PRKCB	Body	chr16
cg05700681	Financial difficulties	-0.31	0.07	1.22E-05	-0.30	0.07	3.58E-05	-0.31	0.07	1.37E-05	-0.30	0.07	4.11E-05	CCL22	1stExon	chr16
cg15247069	Financial difficulties	-0.46	0.11	1.24E-05	-0.47	0.11	1.30E-05	-0.45	0.11	2.38E-05	-0.46	0.11	2.34E-05	ICOS	Body	chr2
cg02387843	Financial difficulties	-0.28	0.06	1.25E-05	-0.27	0.06	4.13E-05	-0.27	0.06	4.09E-05	-0.25	0.07	1.43E-04	SLC2A9	Body	chr4
cg19367172	Financial difficulties	-0.41	0.09	1.25E-05	-0.41	0.09	9.83E-06	-0.39	0.09	3.60E-05	-0.40	0.09	2.60E-05	ST8SIA5	Body	chr18
cg05380127	Financial difficulties	-0.38	0.09	1.27E-05	-0.41	0.09	**3.34E-06**	-0.36	0.09	3.89E-05	-0.39	0.09	1.00E-05	NOTCH4	Body	chr6
cg11391828	Financial difficulties	-0.31	0.07	1.28E-05	-0.32	0.07	1.01E-05	-0.30	0.07	4.35E-05	-0.31	0.07	3.05E-05	KCNE4	TSS1500	chr2
cg19403178	Financial difficulties	-0.44	0.10	1.33E-05	-0.45	0.10	1.01E-05	-0.45	0.10	1.21E-05	-0.46	0.10	9.34E-06		Intergenic	chr1
cg21146652	Financial difficulties	-0.37	0.08	1.33E-05	-0.36	0.08	2.29E-05	-0.34	0.08	6.20E-05	-0.34	0.09	9.46E-05	DGKI	3'UTR	chr7
cg16642360	Financial difficulties	-0.40	0.09	1.34E-05	-0.39	0.09	2.04E-05	-0.41	0.09	1.20E-05	-0.40	0.09	2.37E-05	NOTCH4	Body	chr6
cg06501716	Financial difficulties	-0.21	0.05	1.34E-05	-0.19	0.05	8.51E-05	-0.20	0.05	5.69E-05	-0.18	0.05	3.75E-04	C22orf39	TSS1500	chr22
cg18490350	Financial difficulties	-0.44	0.10	1.34E-05	-0.43	0.10	2.21E-05	-0.42	0.10	3.72E-05	-0.41	0.10	5.89E-05		Intergenic	chr7
cg26950756	Financial difficulties	-0.33	0.08	1.35E-05	-0.32	0.08	2.65E-05	-0.30	0.08	9.95E-05	-0.29	0.08	1.89E-04		Intergenic	chr15
cg07217653	Financial difficulties	-0.23	0.05	1.38E-05	-0.23	0.05	2.71E-05	-0.24	0.05	1.30E-05	-0.23	0.05	2.72E-05	LRRK1	Body	chr15
cg27109056	Financial difficulties	-0.26	0.06	1.43E-05	-0.26	0.06	1.54E-05	-0.24	0.06	8.60E-05	-0.24	0.06	1.13E-04		Intergenic	chr18
cg14971567	Financial difficulties	-0.47	0.11	1.44E-05	-0.46	0.11	3.14E-05	-0.49	0.11	8.23E-06	-0.48	0.11	1.74E-05		Intergenic	chr2
cg15498134	Financial difficulties	-0.26	0.06	1.45E-05	-0.24	0.06	8.21E-05	-0.26	0.06	2.66E-05	-0.23	0.06	1.67E-04	RUNX3	Body	chr1
cg26963277	Financial difficulties	-0.42	0.10	1.47E-05	-0.32	0.09	6.54E-04	-0.43	0.10	9.47E-06	-0.33	0.09	5.00E-04	KCNQ1OT1	TSS1500	chr11
cg08142848	Financial difficulties	-0.37	0.09	1.48E-05	-0.35	0.09	4.25E-05	-0.36	0.09	3.90E-05	-0.34	0.09	1.10E-04	ST3GAL3	TSS1500	chr1

cg14343017	Financial difficulties	-0.32	0.07	1.48E-05	-0.30	0.07	5.69E-05	-0.35	0.07	**2.88E-06**	-0.33	0.07	1.17E-05		Intergenic	chr7
cg10745498	Financial difficulties	-0.32	0.07	1.50E-05	-0.32	0.07	1.89E-05	-0.32	0.07	1.30E-05	-0.32	0.07	1.53E-05	SNX8	Body	chr7
cg00779056	Financial difficulties	-0.41	0.09	1.50E-05	-0.39	0.09	3.74E-05	-0.42	0.09	1.14E-05	-0.40	0.10	3.20E-05		Intergenic	chr16
cg00467296	Financial difficulties	-0.30	0.07	1.51E-05	-0.29	0.07	2.22E-05	-0.27	0.07	7.59E-05	-0.27	0.07	1.34E-04	OR51A7	1stExon	chr11
cg14731400	Financial difficulties	-0.27	0.06	1.52E-05	-0.26	0.06	3.29E-05	-0.27	0.06	2.18E-05	-0.26	0.06	5.45E-05		Intergenic	chr2
cg24323726	Financial difficulties	-0.18	0.04	1.53E-05	-0.17	0.04	6.47E-05	-0.18	0.04	1.90E-05	-0.16	0.04	8.99E-05	ZBED2	TSS200	chr3
cg26687619	Financial difficulties	-0.48	0.11	1.55E-05	-0.47	0.11	2.84E-05	-0.49	0.11	9.91E-06	-0.48	0.11	1.88E-05		Intergenic	chr8
cg23230362	Financial difficulties	-0.40	0.09	1.56E-05	-0.40	0.09	1.67E-05	-0.39	0.09	3.18E-05	-0.39	0.09	3.22E-05	PDZD3	3'UTR	chr11
cg06485892	Financial difficulties	-0.30	0.07	1.60E-05	-0.30	0.07	2.14E-05	-0.29	0.07	4.47E-05	-0.28	0.07	6.78E-05	KHDC1L	3'UTR	chr6
cg03899643	Financial difficulties	-0.22	0.05	1.60E-05	-0.21	0.05	4.62E-05	-0.21	0.05	3.32E-05	-0.20	0.05	1.03E-04		Intergenic	chr1
cg10537176	Financial difficulties	-0.30	0.07	1.60E-05	-0.29	0.07	2.84E-05	-0.26	0.07	1.77E-04	-0.25	0.07	3.71E-04	GPR39	Body	chr2
cg08548559	Financial difficulties	-0.41	0.09	1.62E-05	-0.36	0.09	1.36E-04	-0.37	0.09	1.00E-04	-0.32	0.09	7.29E-04	PIK3IP1	Body	chr22
cg15489422	Financial difficulties	-0.47	0.11	1.65E-05	-0.46	0.11	3.41E-05	-0.49	0.11	1.17E-05	-0.48	0.11	2.57E-05	TMCC1	5'UTR	chr3
cg08720250	Financial difficulties	-0.27	0.06	1.66E-05	-0.26	0.06	2.99E-05	-0.25	0.06	7.86E-05	-0.24	0.06	1.48E-04		Intergenic	chr12
cg02433979	Financial difficulties	-0.30	0.07	1.67E-05	-0.29	0.07	2.90E-05	-0.29	0.07	2.66E-05	-0.28	0.07	5.90E-05		Intergenic	chr7
cg04875821	Financial difficulties	-0.31	0.07	1.70E-05	-0.30	0.07	3.59E-05	-0.32	0.07	1.15E-05	-0.31	0.07	2.31E-05		Intergenic	chr15
cg17173767	Financial difficulties	0.37	0.08	1.76E-05	0.37	0.09	1.71E-05	0.35	0.09	5.96E-05	0.35	0.09	4.52E-05	C8orf84	1stExon	chr8
cg00811166	Financial difficulties	-0.47	0.11	1.76E-05	-0.47	0.11	2.21E-05	-0.50	0.11	7.09E-06	-0.50	0.11	9.86E-06	TERT	Body	chr5
cg09589308	Financial difficulties	-0.31	0.07	1.76E-05	-0.30	0.07	3.58E-05	-0.27	0.07	1.63E-04	-0.26	0.07	3.14E-04	KCNH8	Body	chr3
cg16640008	Financial difficulties	-0.30	0.07	1.77E-05	-0.28	0.07	7.11E-05	-0.31	0.07	1.52E-05	-0.29	0.07	6.85E-05		Intergenic	chr6
cg25930161	Financial difficulties	-0.39	0.09	1.77E-05	-0.38	0.09	2.95E-05	-0.40	0.09	1.50E-05	-0.38	0.09	3.16E-05	ADAMTS2	Body	chr5
cg04688596	Financial difficulties	-0.32	0.07	1.80E-05	-0.32	0.07	1.46E-05	-0.32	0.07	1.90E-05	-0.32	0.07	1.88E-05	FBN3	Body	chr19
cg02674639	Financial difficulties	-0.26	0.06	1.81E-05	-0.25	0.06	4.15E-05	-0.24	0.06	9.62E-05	-0.23	0.06	2.08E-04	WASF3	5'UTR	chr13
cg13362105	Occupational trajectories	-0.61	0.11	5.52E-08	-0.61	0.11	**8.61E-08**	-0.62	0.11	**4.66E-08**	-0.61	0.11	**6.56E-08**	BBS9	TSS200	chr7
cg11722699	Occupational trajectories	0.43	0.08	1.34E-07	0.41	0.08	**3.47E-07**	0.43	0.08	**1.16E-07**	0.42	0.08	**3.08E-07**	DSC3	TSS200	chr18
cg14089425	Occupational trajectories	-0.45	0.09	3.74E-07	-0.46	0.09	**3.37E-07**	-0.46	0.09	**2.96E-07**	-0.46	0.09	**2.53E-07**	KCNQ1	Body	chr11
cg27431274	Occupational trajectories	-0.43	0.09	4.84E-07	-0.42	0.09	**8.76E-07**	-0.43	0.08	**4.25E-07**	-0.42	0.08	**8.09E-07**	BTBD11	Body	chr12
cg06881239	Occupational trajectories	-0.42	0.08	5.50E-07	-0.42	0.08	**6.62E-07**	-0.41	0.08	**6.71E-07**	-0.41	0.08	**8.00E-07**	PIRT	TSS200	chr17
cg06803821	Occupational trajectories	-0.57	0.11	6.68E-07	-0.58	0.11	**6.61E-07**	-0.57	0.11	**9.09E-07**	-0.57	0.11	**9.51E-07**		Intergenic	chr16

SEP, Indicator of socioeconomic position; CMD: cardiometabolic disorders (obesity, diabetes, hypertension, coronary heart disease); HB, health behaviors (smoking, sedentary behavior, hazardous alcohol intake)

[a] Linear regression models for the association between life-course SEP indicators (predictor, lowest versus highest) and methylation of CpG markers (outcome), adjusted for sex, age, seasonality of blood collection, PBMC composition, and chip (BH significance threshold)

[b] Linear regression models for the association between life-course SEP indicators (predictor, lowest versus highest) and methylation of CpG markers (outcome), additionally adjusted for health behaviors
Statistical significance was set according to Benjamini-Hochberg threshold

[c] Linear regression models for the association between life-course SEP indicators (predictor, lowest versus highest) and methylation of CpG markers (outcome), additionally adjusted for cardiometabolic disorders
Statistical significance was set according to Benjamini-Hochberg threshold

[d] Linear regression models for the association between life-course SEP indicators (predictor, lowest versus highest) and methylation of CpG markers (outcome), additionally adjusted for health behaviors and cardiometabolic disorders
Statistical significance was set according to Benjamini-Hochberg threshold

[e] **P-values displayed in bold** indicate a significant association (Benjamini-Hochberg) in the model additionally adjusted for health behaviors and/or cardiometabolic disorders

[f] Intragenic regions: UTR, Untranslated region (intron); TSS200, Distance (i.e. 200 bp) to **T**ranscription **S**tart **S**ite (promoter); Body, Gene body (exon).
Intergenic regions: CpG is not located within a known gene

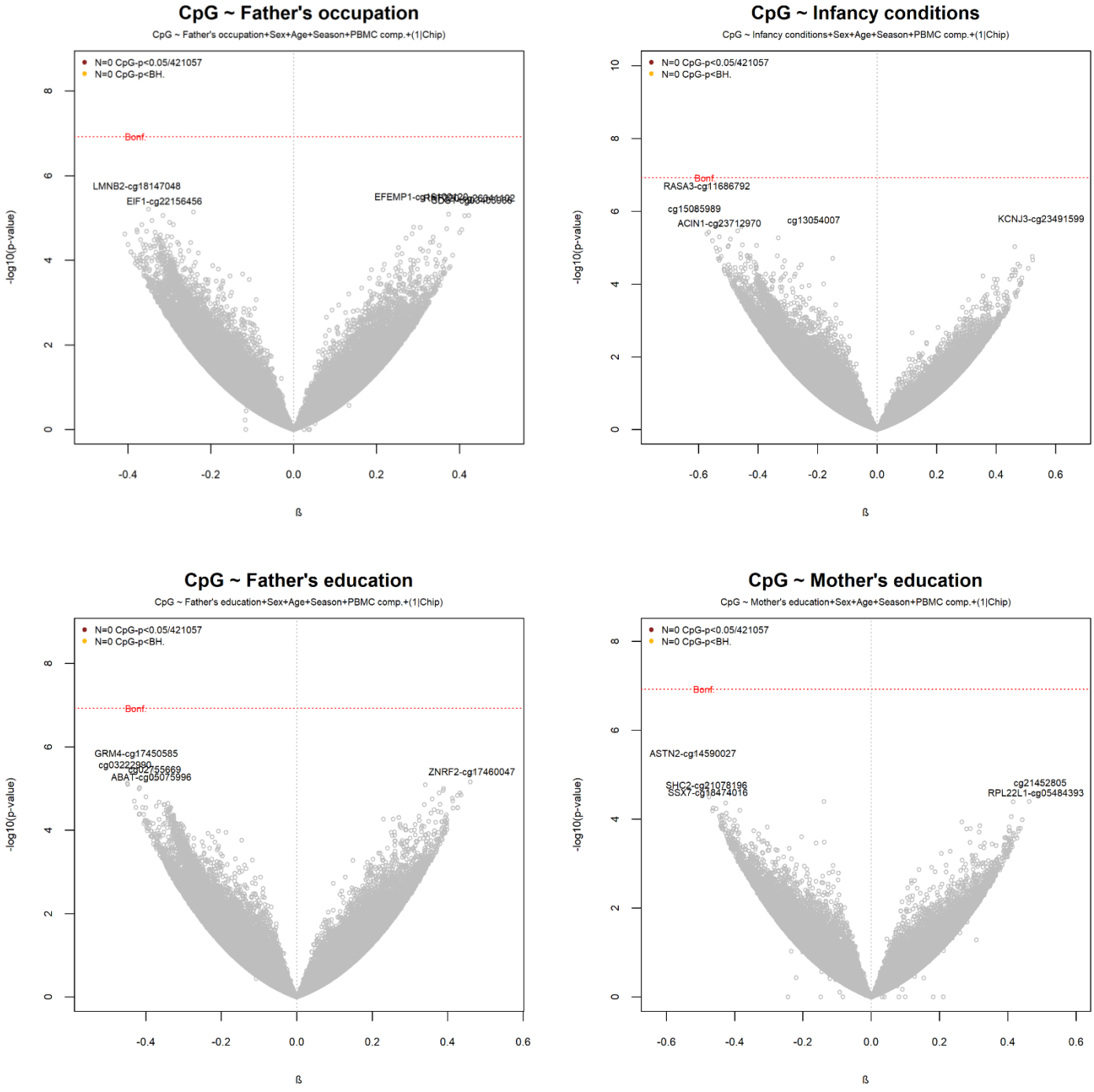
Table 3: Top 30 Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways identified based on CpG markers associated with life-course SEP indicators (N=161, Table 1)

GO	Ontology	GO pathway	GO P-value	KEGG	KEGG pathway	KEGG P-Value
GO:0046959	BP	habituation	<0.001	hsa00563	Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	0.010
GO:0030506	MF	ankyrin binding	<0.001	hsa05200	Pathways in cancer	0.017
GO:0060372	BP	regulation of atrial cardiac muscle cell membrane repolarization	<0.001	hsa05340	Primary immunodeficiency	0.022
GO:1902533	BP	positive regulation of intracellular signal transduction	<0.001	hsa05231	Choline metabolism in cancer	0.023
GO:0016192	BP	vesicle-mediated transport	<0.001	hsa04672	Intestinal immune network for IgA production	0.037
GO:0005886	CC	plasma membrane	<0.001	hsa04015	Rap1 signaling pathway	0.041
GO:0005887	CC	integral component of plasma membrane	0.001	hsa00740	Riboflavin metabolism	0.048
GO:0016528	CC	sarcoplasm	0.001	hsa04514	Cell adhesion molecules (CAMs)	0.061
GO:0086014	BP	atrial cardiac muscle cell action potential	0.001	hsa05221	Acute myeloid leukemia	0.062
GO:0031639	BP	plasminogen activation	0.002	hsa05223	Non-small cell lung cancer	0.062
GO:0045766	BP	positive regulation of angiogenesis	0.002	hsa04971	Gastric acid secretion	0.078
GO:0098915	BP	membrane repolarization during ventricular cardiac muscle cell action potential	0.002	hsa00533	Glycosaminoglycan biosynthesis - keratan sulfate	0.083
GO:0003779	MF	actin binding	0.003	hsa04610	Complement and coagulation cascades	0.085
GO:0045599	BP	negative regulation of fat cell differentiation	0.004	hsa00604	Glycosphingolipid biosynthesis - ganglio series	0.088
GO:0030247	MF	polysaccharide binding	0.004	hsa00730	Thiamine metabolism	0.094
GO:0051571	BP	positive regulation of histone H3-K4 methylation	0.004	hsa05202	Transcriptional misregulation in cancer	0.107
GO:0086005	BP	ventricular cardiac muscle cell action potential	0.004	hsa04060	Cytokine-cytokine receptor interaction	0.108
GO:0030902	BP	hindbrain development	0.004	hsa00770	Pantothenate and CoA biosynthesis	0.111
GO:0042730	BP	fibrinolysis	0.005	hsa04062	Chemokine signaling pathway	0.111
GO:0043034	CC	costamere	0.005	hsa04666	Fc gamma R-mediated phagocytosis	0.112
GO:0043113	BP	receptor clustering	0.005	hsa04070	Phosphatidylinositol signaling system	0.124
GO:0097503	BP	sialylation	0.005	hsa04061	Viral protein interaction with cytokine and cytokine receptor	0.126
GO:0044325	MF	ion channel binding	0.006	hsa00514	Other types of O-glycan biosynthesis	0.127
GO:0000225	MF	N-acetylglucosaminylphosphatidylinositol deacetylase activity	0.006	hsa04972	Pancreatic secretion	0.13
GO:0000416	BP	positive regulation of histone H3-K36 methylation	0.006	hsa00515	Mannose type O-glycan biosynthesis	0.132
GO:0002517	BP	T cell tolerance induction	0.006	hsa03060	Protein export	0.132
GO:0008118	MF	N-acetyllactosaminide alpha-2,3-sialyltransferase activity	0.006	hsa00790	Folate biosynthesis	0.148
GO:0019778	MF	Atg12 activating enzyme activity	0.006	hsa04670	Leukocyte transendothelial migration	0.151
GO:0021508	BP	floor plate formation	0.006	hsa04725	Cholinergic synapse	0.151
GO:0022616	BP	DNA strand elongation	0.006	hsa00601	Glycosphingolipid biosynthesis - lacto and neolacto series	0.154

BP, Biological process; CC, Cellular component; MF, Molecular Function

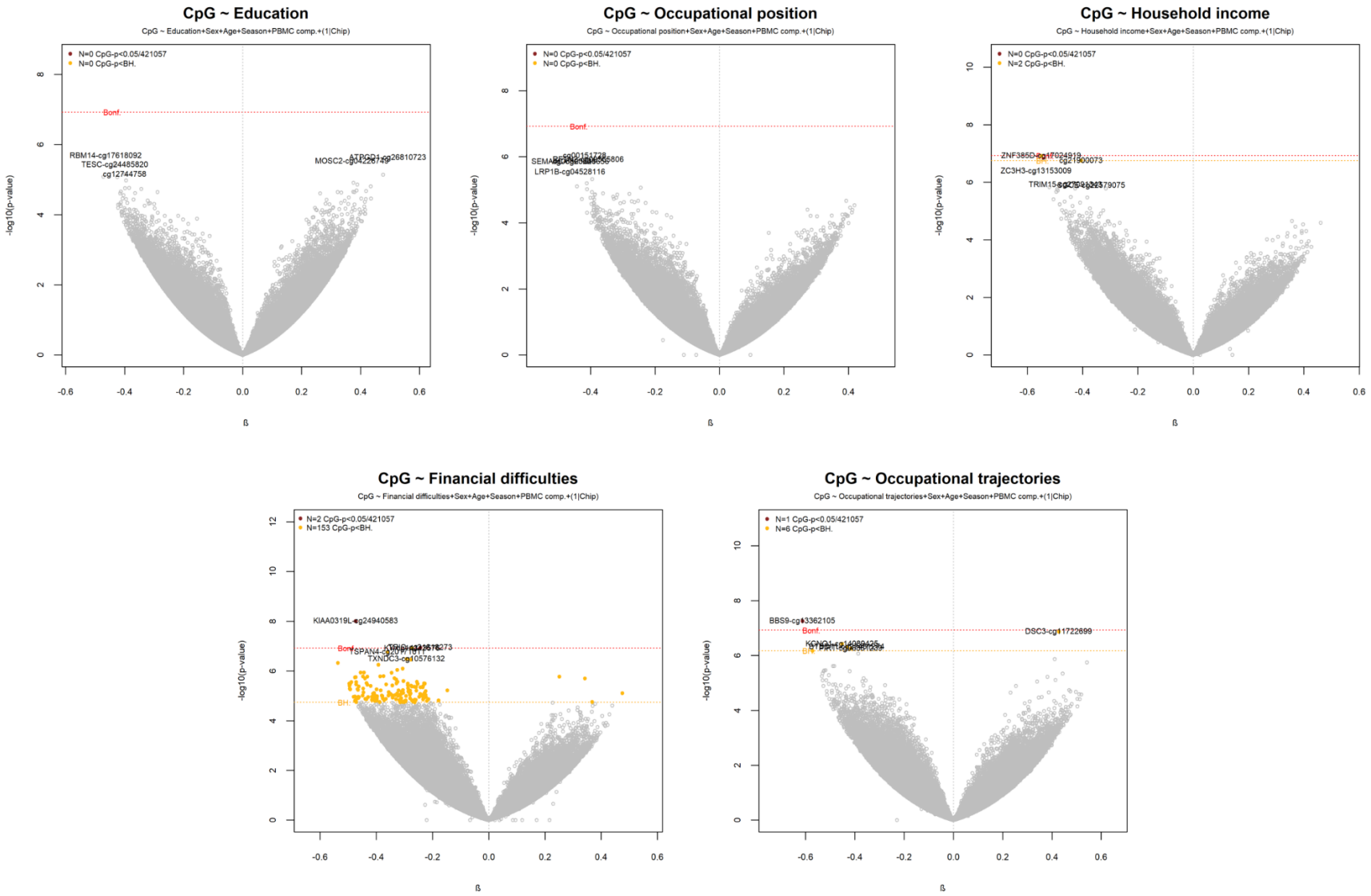
[a] Significance threshold was set at P-value <0.05

Figure 1: Funnel plots for the associations between early-life SEP indicators and genome-wide CpG markers, adjusted for main covariates (M1)



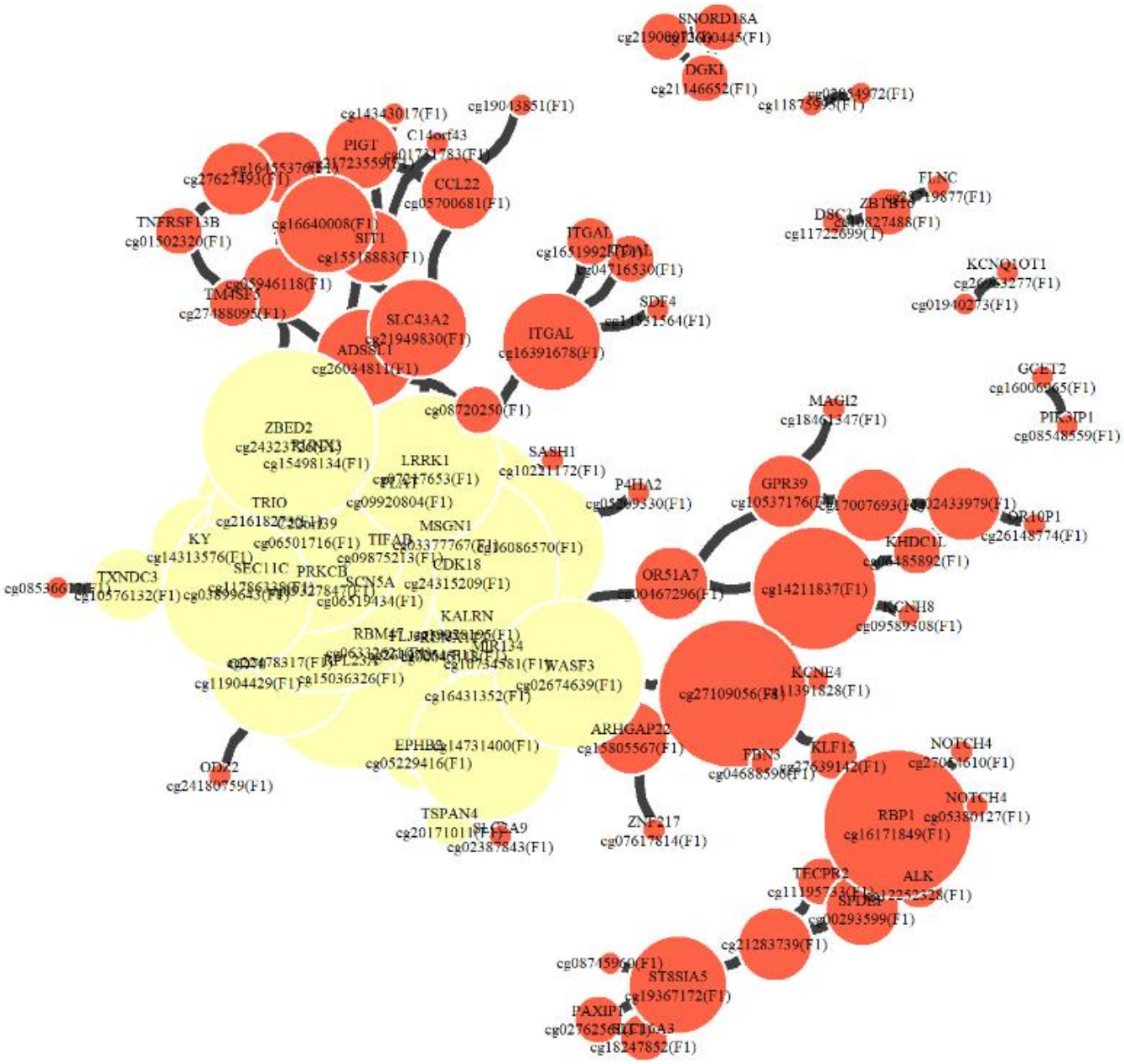
Beta, mean methylation difference (low vs. high SEP)
Linear regression model for the association between early-life SEP indicators (predictor, lowest versus highest) and methylation of CpG markers (outcome), adjusted for sex, age, seasonality of blood collection, PBMC composition, and chip (random effect variable)

Figure 2: Funnel plots for the associations between SEP indicators in adulthood and genome-wide CpG markers, adjusted for main covariates (M1)



Beta, mean methylation difference (low vs. high SEP)
Linear regression model for the association between SEP indicators in adulthood (predictor, lowest versus highest) and methylation of CpG markers (outcome), adjusted for sex, age, seasonality of blood collection, PBMC composition, and chip (random effect variable)

Figure 3: Network of interrelated CpG markers associated with at least one indicator of SEP, and related to at least one other CpG, displayed according to clusters (Cluster 1: N=62 CpGs – red; Cluster 2: N=29 – yellow).



(FO); father's occupation; (IC), infancy conditions; (FE), father's education; (ME), mother's education; (E), participant's education, (O), occupational position in adulthood; (I), Household income; (F1), Financial difficulties; (T), Occupational trajectories

CpGs were identified from linear regression models for the association between SEP indicators (predictor, lowest versus highest) and methylation of CpG markers (outcome), adjusted for sex, age, seasonality of blood collection, PBMC composition, chip (random effect variable)

Of the 161 significantly associated CpGs (Table 1), only CpGs that were associated with at least one other CpG (N=91) were included in the network. Each circle represents a CpG, whereby the size of the circle is related to the centrality of the CpG; the bigger the circle, the more relations to other CpGs there are.

Supplementary Table 1: Fisher's exact test for the association between CpG methylation status and SEP indicators

	Financial difficulties	Household income	Occupational trajectories
Hypermethylation	4	0	1
Hypomethylation	149	2	5

Fisher's test p=0.2275

Supplementary Table 2: Fisher's exact test for the association between CpG methylation status and CpG location (detailed)

	1stExon	3'UTR	5'UTR	Body	Intergenic	TSS
Hypermethylation	1	0	1	1	0	2
Hypomethylation	6	5	10	72	41	22

Fisher's test p=0.063

Supplementary Table 3: Fisher's exact test for the association between CpG methylation status and CpG location (grouped)

	Intergenic	Intragenic
Hypermethylation	0	5
Hypomethylation	41	115

Fisher's test p=0.330

Supplementary Table 4: Fisher's exact test for the association between SEP indicators CpG location (detailed)

	1stExon	3'UTR	5'UTR	Body	Intergenic	TSS
Financial difficulties	7	5	11	70	39	21
Household income	0	0	0	1	1	0
Occupational trajectories	0	0	0	2	1	3

Fisher's test p=0.6641

Supplementary Table 5: Fisher's exact test for the association between SEP indicators CpG location (grouped)

	Intergenic	Intragenic
Financial difficulties	39	114
Household income	1	1
Occupational trajectories	1	5

Fisher's test p=0.634

Supplementary Table 6: Fisher's exact test for the association between network-identified clusters and CpG methylation status

	Hypermethylation	Hypomethylation
Cluster 1	2	60
Cluster 2	0	29

Fisher's test p=1

Supplementary Table 7: Fisher's exact test for the association between network-identified clusters and SEP indicators

	Financial difficulties	Household income	Occupational trajectories
Cluster 1	60	1	1
Cluster 2	29	0	0

Fisher's test p=0.1

Supplementary Table 8: Fisher's exact test for the association between network-identified clusters and CpG location (detailed)

	1stExon	3'UTR	5'UTR	Body	Intergenic	TSS
Cluster 1	4	3	2	28	18	7
Cluster 2	0	0	3	14	5	7

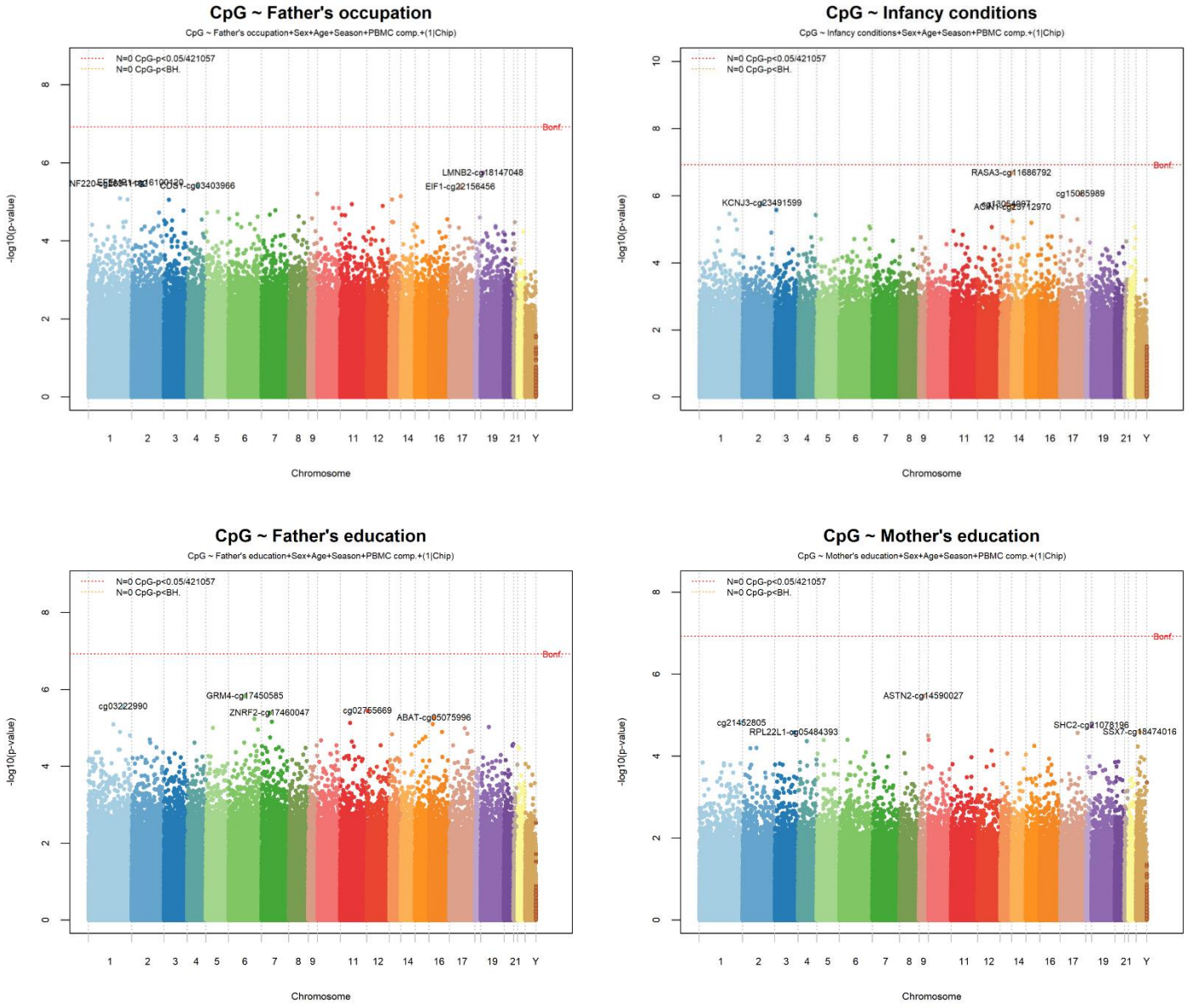
Fisher's test p=0.159

Supplementary Table 9: χ^2 test for the association between network-identified clusters and CpG location (grouped)

	Intragenic	Intergenic
Cluster 1	44	18
Cluster 2	24	5

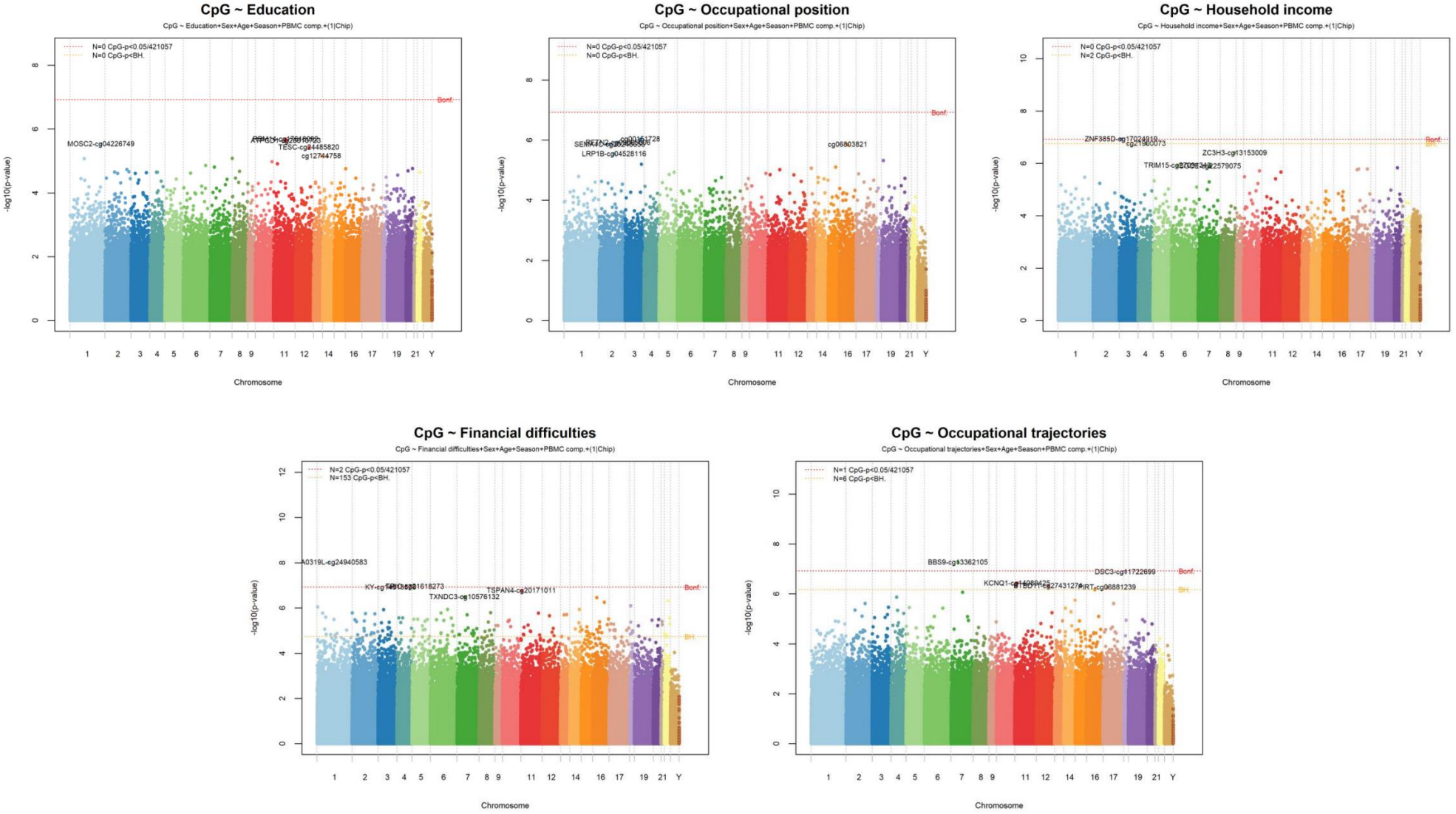
Fisher's test p=0.303

Supplementary Figure 1: Manhattan plots for the associations between early-life SEP indicators and genome-wide CpG markers, adjusted for main covariates (M1)



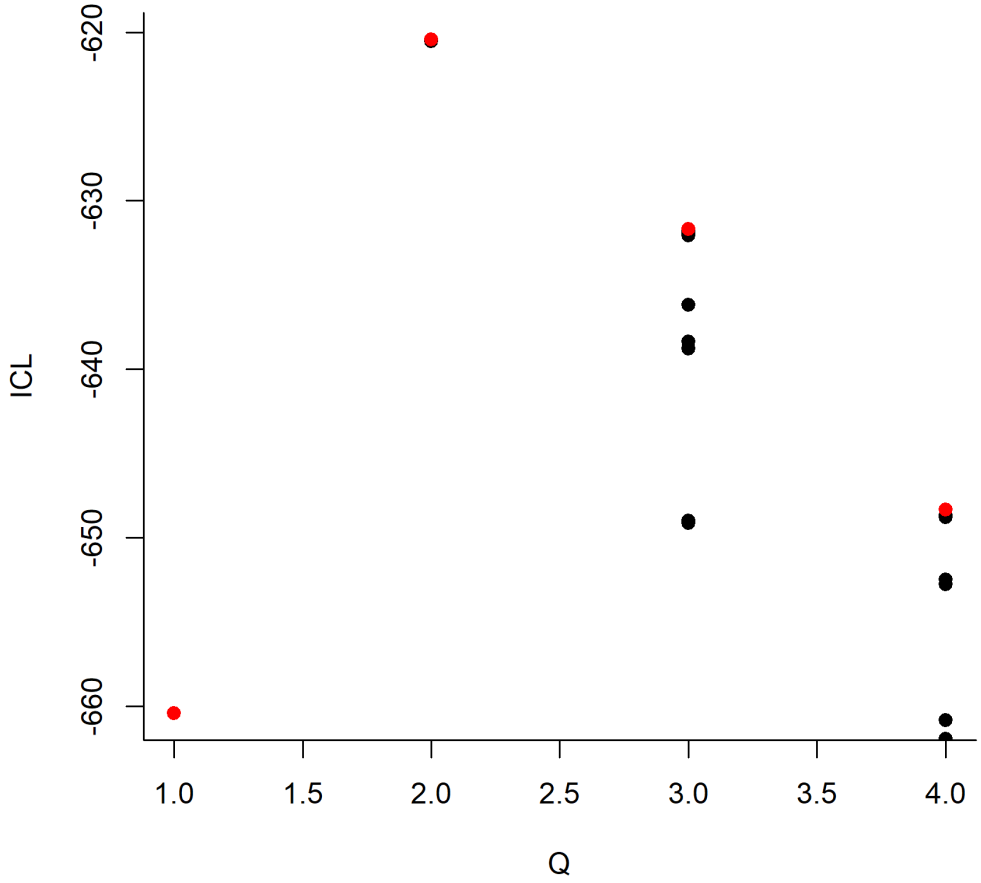
Linear regression model for the association between SEP indicators in early-life (predictor, lowest versus highest) and methylation of CpG markers (outcome), adjusted for sex, age, seasonality of blood collection, PBMC composition, and chip (random effect variable)

Supplementary Figure 2: Manhattan plots for the associations between SEP indicators in adulthood and genome-wide CpG markers, adjusted for main covariates (M1)



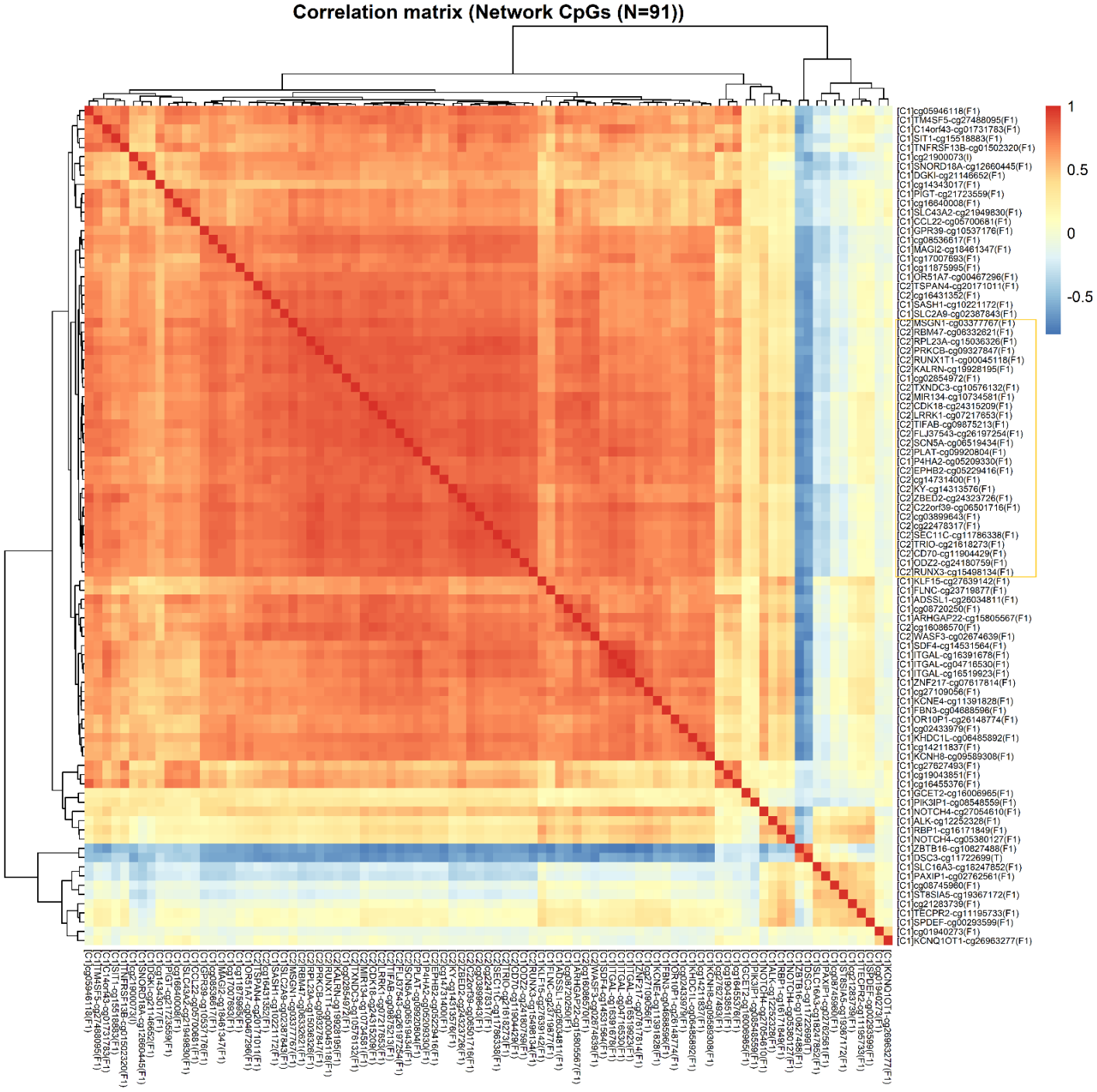
Linear regression model for the association between SEP indicators in adulthood (predictor, lowest versus highest) and methylation of CpG markers, adjusted for sex, age, seasonality of blood collection, PBMC composition, and chip (random effect variable)

Supplementary Figure 3: ICL criterion plot for the determination of the number of clusters (Q) based on SEP-related CpG markers (Table 2). The optimal number of clusters Q is determined by the maximum ICL value (Q=2)



ICL, Integrated Completed Likelihood
Optimal number of clusters Q is determined by the maximum ICL value

Supplementary Figure 4: Correlation heatmap of 91SEP-related CpGs included in the partial correlation network (Figure 3)



[C1], Cluster 1; [C2], Cluster 2 (legend-yellow square)
(FO); father's occupation; (IC), infancy conditions; (FE), father's education; (ME), mother's education; (E), participant's education, (O), occupational position in adulthood; (I), Household income; (F1), Financial difficulties; (T), Occupational trajectories
Of the 161 SEP-related CpGs (Table 1), only CpGs that were associated with at least one other CpGs (N=91) were included in the network and the correlation heatmap.

Annex I: Reporting and grouping life-course SEP indicators

Early-life SEP indicators (self-reported)

There were 10 suggested categories for father's occupational position that were subsequently grouped into three categories: "High" (superior manager, liberal professions, CEO-director, professor), "Middle" (qualified non-manual worker, middle-level executive, self-employed worker (craftsman/trade)), "Low" (unqualified manual worker, qualified manual worker, farmer, unqualified non-manual worker). Mother and father's education were available in 10 suggested categories that were classified into three groups: "High" (university education superior education (+3 years after high school – "maturité")), "Middle" (high school – "maturité", education preparing for a profession: apprenticeship – "CFC"), "Low" (mandatory education, trade school diploma). Material and financial condition in infancy inquired about whether participants had or benefited from the following items/activities during their childhood: car, TV, a domestic worker, dishwasher, telephone, enough heat at home, participating to a social or cultural association, leaving home during annual vacation, home ownership. Owing ≥7 items was classified as "High", 4-6 items was classified as "Middle", and ≤3 items was classified as "Low" infancy conditions.

SEP indicators in adulthood and trajectories (self-reported)

Own last known occupational position was self-reported and further classified into three categories: "High" (managers: liberal professions, directors and professors), "Middle" (lower level executives: teachers, qualified technicians, and nurses), "Low" (low qualified non-manuals and manuals: sales-assistants, clerks and manual workers). Own education was defined in the same way as father's and mother's education. Financial difficulties inquired whether the participant would face difficulties paying food, rent, charges, insurance, loans throughout the month, and was classified as following: "No difficulties" ("*This has never happened")*, "Average difficulties" (*"Not currently, but this has happened in the past)*, "Important difficulties" (*"This has happened in the recent past"*). Occupational trajectories across the life-course were classified as following : "Stable high" (high father's occupation and high own occupation), "Upward" (low father's occupation and middle/high own occupation, or middle father's occupation and high own occupation), "Stable middle" (middle father's occupation, middle own occupation), "Downward" (high father's occupation and middle/low own occupation, or middle father's occupation and low own occupation), "Stable low" (low father's occupation and low own occupation).

Annex II: Reporting and grouping health behaviors and history of cardiometabolic disorders

Health behaviors (self-reported)

Smoking status was categorized as current and non-current smokers, the latter category including former smokers. Alcohol intake was measured using questions on the number of alcoholic drinks usually consumed within a week and categorized as hazardous drinking (>3 daily alcoholic drinks for men; >2 daily alcoholic drinks for women) versus non-hazardous drinking. Physical activity was reported on a scale from 1 to 10, 1 corresponding to a complete sedentary lifestyle and 10 corresponding to manual work combined with sports practice. Based on this scale, three categories were subsequently defined: "Low" (1–4), "Middle" (5), and "High" (6–10).

Cardiometabolic disorders

Obesity status was defined as having a BMI≥30 kg/m^2 at clinical visit. Hypertension was based on self-reported hypertension, self-reported use of anti-hypertensive drugs, or having a systolic blood pressure ≥140mmHg *and* a diastolic blood pressure ≥90mmHg at clinical visit. Diabetes was based on self-reported diabetes, self-reported use of anti-diabetic drugs, having a blood sugar ≥7mmol/L at clinical visit, or having a glycated hemoglobin ≥6.5% (fasting conditions). Coronary heart disease was based on self-reporting a history of myocardial infarction, angina, or ischemic artery disease.

References

1. Marmot, M. and R. Wilkinson, *Social determinants of health*. 2005: OUP Oxford.
2. Wolfe, B., W. Evans, and T.E. Seeman, *The biological consequences of socioeconomic inequalities*. 2012: Russell Sage Foundation.
3. Stringhini, S., et al., *Socioeconomic status and the 25× 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1· 7 million men and women.* The Lancet, 2017. **389**(10075): p. 1229-1237.
4. Petrovic, D., et al., *Sociodemographic, behavioral and genetic determinants of allostatic load in a Swiss population-based study.* Psychoneuroendocrinology, 2016. **67**: p. 76-85.
5. Stringhini, S., et al., *Life-course socioeconomic status and DNA methylation of genes regulating inflammation.* International journal of epidemiology, 2015. **44**(4): p. 1320-1330.
6. Needham, B.L., et al., *Life course socioeconomic status and DNA methylation in genes related to stress reactivity and inflammation: The multi-ethnic study of atherosclerosis.* Epigenetics, 2015. **10**(10): p. 958-969.
7. Fraga, S., et al., *Association of socioeconomic status with inflammatory markers: a two cohort comparison.* Preventive medicine, 2015. **71**: p. 12-19.
8. Bird, A., *DNA methylation patterns and epigenetic memory*. Genes & development, 2002. **16**(1): p. 6-21.
9. Campbell, N.A. and J.B. Reece, *Biology. 7th.* Ed Pearson Benjamin Cummings. Cape Town, 2005.
10. Guida, F., et al., *Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation.* Human molecular genetics, 2015. **24**(8): p. 2349-2359.
11. Mostafavi, N., et al., *Acute changes in DNA methylation in relation to 24 h personal air pollution exposure measurements: A panel study in four European countries.* Environment international, 2018. **120**: p. 11-21.
12. Tobi, E.W., et al., *DNA methylation differences after exposure to prenatal famine are common and timing-and sex-specific.* Human molecular genetics, 2009. **18**(21): p. 4046-4053.
13. Barres, R., et al., *Acute exercise remodels promoter methylation in human skeletal muscle.* Cell metabolism, 2012. **15**(3): p. 405-411.
14. King, K.E., et al., *Neighborhood and family environment of expectant mothers may influence prenatal programming of adult cancer risk: discussion and an illustrative DNA methylation example.* Biodemography and social biology, 2016. **62**(1): p. 87-104.
15. Chi, G.C., et al., *Long-term outdoor air pollution and DNA methylation in circulating monocytes: results from the Multi-Ethnic Study of Atherosclerosis (MESA).* Environmental Health, 2016. **15**(1): p. 119.
16. King, K., S. Murphy, and C. Hoyo, *Epigenetic regulation of Newborns' imprinted genes related to gestational growth: patterning by parental race/ethnicity and maternal socioeconomic status.* J Epidemiol Community Health, 2015. **69**(7): p. 639-647.
17. Borghol, N., et al., *Associations with early-life socio-economic position in adult DNA methylation.* International journal of epidemiology, 2011. **41**(1): p. 62-74.
18. Petrovic, D., et al., *Relation of 24-hour urinary caffeine and caffeine metabolite excretions with self-reported consumption of coffee and other caffeinated beverages in the general population.* Nutrition & metabolism, 2016. **13**(1): p. 81.
19. Hastie, T., et al., *Imputing missing data for gene expression arrays*. 1999.
20. Houseman, E.A., et al., *DNA methylation arrays as surrogate measures of cell mixture distribution.* BMC bioinformatics, 2012. **13**(1): p. 86.
21. Chadeau-Hyam, M., et al., *Deciphering the complex: Methodological overview of statistical models to derive OMICS-based biomarkers.* Environmental and molecular mutagenesis, 2013. **54**(7): p. 542-557.
22. Phipson, B., J. Maksimovic, and A. Oshlack, *missMethyl: an R package for analyzing data from Illumina's HumanMethylation450 platform.* Bioinformatics, 2015. **32**(2): p. 286-288.

23. Thomas, P.D., et al., *PANTHER: a library of protein families and subfamilies indexed by function.* Genome research, 2003. **13**(9): p. 2129-2141.
24. Chiquet, J., et al., *Simone: Statistical inference for modular networks.* Bioinformatics, 2008. **25**(3): p. 417-418.
25. Miller, G.E., et al., *Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling.* Proceedings of the National Academy of Sciences, 2009. **106**(34): p. 14716-14721.
26. Tung, J., et al., *Social environment is associated with gene regulatory variation in the rhesus macaque immune system.* Proceedings of the National Academy of Sciences, 2012. **109**(17): p. 6490-6495.
27. Stringhini, S., et al., *Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study.* PLoS medicine, 2013. **10**(7): p. e1001479.
28. Hansson, G.K., *Inflammation, atherosclerosis, and coronary artery disease.* New England Journal of Medicine, 2005. **352**(16): p. 1685-1695.
29. Colotta, F., et al., *Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability.* Carcinogenesis, 2009. **30**(7): p. 1073-1081.
30. Dunn, B.K., et al., *Health disparities in breast cancer: biology meets socioeconomic status.* Breast cancer research and treatment, 2010. **121**(2): p. 281-292.
31. Marmot, M., *The health gap: the challenge of an unequal world.* The Lancet, 2015. **386**(10011): p. 2442-2444.
32. McGuinness, D., et al., *Socio-economic status is associated with epigenetic differences in the pSoBid cohort.* International journal of epidemiology, 2012. **41**(1): p. 151-160.
33. Zhang, Y. and H. Lu, *Signaling to p53: ribosomal proteins find their way.* Cancer cell, 2009. **16**(5): p. 369-377.
34. Fattaey, A., et al., *Characterization of the retinoblastoma binding proteins RBP1 and RBP2.* Oncogene, 1993. **8**(11): p. 3149-3156.
35. Tehranifar, P., et al., *Early life socioeconomic factors and genomic DNA methylation in mid-life.* Epigenetics, 2013. **8**(1): p. 23-27.
36. Kuh, D., et al., *Life course epidemiology.* Journal of epidemiology and community health, 2003. **57**(10): p. 778.
37. Batty, G.D., et al., *Accuracy of adults' recall of childhood social class: findings from the Aberdeen children of the 1950s study.* Journal of Epidemiology & Community Health, 2005. **59**(10): p. 898-903.
38. Adalsteinsson, B.T., et al., *Heterogeneity in white blood cells has potential to confound DNA methylation measurements.* PloS one, 2012. **7**(10): p. e46705.

General discussion

Summary of main results

The main objective of this thesis was to investigate the role of multiple intermediate factors and biological processes underlying the life-course socioeconomic gradient in cardiometabolic disorders (CMD). In the first study, we systematically examined all previous research assessing the role of health behaviors to socioeconomic differences in cardiometabolic disorders and all-cause mortality, and found that this contribution varied according to social, economic, and cultural factors. Then, we explored the role of sleep duration as another mechanism underlying the life-course socioeconomic gradient in cardiovascular outcomes using multi-cohort data on 111'205 individuals, and found that excessively short sleep meaningfully contributed to this relationship. Finally, we examined the relationship between life-course socioeconomic position (SEP) and DNA methylation as an underexplored molecular mechanisms through which the social environment "gets embedded" under the skin, and found that adverse socioeconomic conditions in adulthood lead to a differential methylation of markers involved in immune, inflammatory, and cancer-related processes.

Comparison to the literature

In chapter 1, we performed a systematic review of the literature investigating the contribution of health behaviors to socioeconomic differences in all-cause mortality and cardiometabolic disorders. The purpose of this research was to provide a comprehensive synthesis on the role of health behaviors and to identify the factors determining the differential contribution of health behaviors in given contexts [1]. Overall, we observed a strong socioeconomic gradient in health outcomes across the included articles, whereby adverse socioeconomic circumstances were consistently associated with an increased risk of cardiometabolic disorders and all-cause mortality. Furthermore, we found that the contribution of health

behaviors to this association varied according to geographic regions, demographic characteristics of included participants, the type of health behaviors and outcomes, and study characteristics. We identified three major explanations for the differential contribution of health behaviors. First, *the differential social patterning of health behaviors* accounts for the most important determinants of the heterogeneous contribution of health behaviors, and is strongly related to the epidemiologic transition of cardiometabolic disorders and associated risk factors, shifting from the higher towards the lower socioeconomic groups [2, 3]. According to this model, this transition has started at different periods and has progressed at a different pace across geographic regions and for men and women, eventually yielding different socioeconomic gradients in health behaviors and cardiometabolic diseases [1-4]. Second, we found that *physiological factors* may also determine the differential contribution of health behaviors, whereby certain behaviors explain a greater proportion of the socioeconomic gradient as they are causally more related to a given health outcome (i.e. smoking and cardiovascular diseases, dietary patterns and obesity) [5, 6]. Third, *the methodological characteristics of included studies* can also explain the heterogeneous contribution of health behaviors across included articles, whereby a repeated assessment of health behaviors was generally found to explain a greater proportion of the socioeconomic gradient in cardiometabolic disorders, as in longitudinal studies [7]. In summary, this study systematically examined *all* previous research addressing the role of health behaviors to the socioeconomic differences in cardiometabolic disorders and all-cause mortality, and provided a comprehensive synthesis on the factors and mechanisms influencing the contribution of health behaviors to this gradient.

In chapter 2, we investigated the role of sleep duration in the association between life-course socioeconomic position and cardiovascular outcomes, using data from eight European

cohorts. The objective of this study was to assess the contribution of sleep duration as an additional intermediate factor to the life-course socioeconomic gradient, as poor sleep was found to be driven by adverse socioeconomic circumstances, but also to be strongly associated with cardiometabolic disorders [8-10]. In line with previous research, we found a strong life-course socioeconomic gradient in coronary heart disease (CHD), whereby adverse socioeconomic circumstances in early-life and in adulthood were associated with an increased cardiovascular risk [1]. We also observed a meaningful association between low socioeconomic position across the life-course and abnormal sleeping patterns. These results are explained by the socioeconomic patterning of sleep duration, and are consistent with previous research showing that disadvantaged individuals experience greater sleep problems due to adverse early-life experiences, shift work, financial and material difficulties, and chronic stress [8, 9, 11]. Furthermore, we found an association between abnormal sleeping patterns and an increased risk of coronary heart disease and stroke, with short sleep being a stronger risk factor for coronary heart disease than excessively long sleep. This relation has been systematically reported by previous experimental and clinical studies, whereby sleep deprivation was found to disrupt key physiological processes often resulting in a higher cardiovascular risk, whereas long sleep was generally found to occur as a consequence of preexisting disorders [10, 12]. Finally, we found that short sleep duration significantly contributed to the associations between life-course socioeconomic position and coronary heart disease, explaining up to 13% of the gradient. In summary, this study showed a meaningful contribution of sleep to the life-course socioeconomic gradient in cardiovascular disorders, further contributing to the understanding of intermediate mechanisms underlying the socioeconomic gradient in cardiometabolic disorders.

In chapter 3, we explored the relation between life-course SEP and the differential methylation of genome-wide CpG markers. The purpose of this study was to explore the effect of adverse socioeconomic circumstances on subclinical, "inner layer" biological processes (Figure 2 – Introduction), and to investigate how these modifications potentially translate into a higher disease risk. We found that low SEP in adulthood was associated with a decreased methylation (hypomethylation) of a large number of genome-wide CpGs (N=161), in line with previous research [13, 14]. Socioeconomic factors in early life were conversely not associated with the differential methylation of CpG markers. These results may be related to a smaller effect size between early-life SEP and DNA methylation in adulthood, due to a biased, retrospective self-reporting of childhood SEP [13, 15]. Furthermore, we found that a substantial proportion of the association between socioeconomic position and CpG methylation was explained by variations in health behaviors and/or cardiometabolic disorders, with only 33 out of 161 CpGs (20%) being related to SEP independently from health behaviors and cardiometabolic disorders. Furthermore, we found that the identified CpGs were involved in immune and inflammation-related processes, which is consistent with former findings, as adverse socioeconomic circumstances have been previously related to immune-related CpG markers and aberrant inflammation, eventually leading to the occurrence of serious chronic illnesses such as diabetes, heart disease, and cancer [16-19]. In summary, this study showed that adverse socioeconomic circumstances are strongly related to a modified epigenetic signature of markers involved in immune and inflammatory pathways; however, further investigations are required to determine the exact physiological effects of these alterations.

Strengths and limitations

The studies presented in this thesis have several strengths. Overall, the systematic review, the multi-cohort counterfactual mediation analysis, and the epigenome-wide analysis applied innovative methodological approaches to examine central yet poorly described mechanisms underlying the socioeconomic gradient in cardiometabolic disorders. First, in the systematic review, we examined *all* previously published articles and synthesized their findings according to specifically defined procedures, which allowed us to identify major mechanisms driving the differential contribution of health behaviors [20, 21]. Second, we used a very large multi-cohort sample to assess the contribution of sleep as an additional, unexplored mechanism underlying the life-course socioeconomic gradient in cardiovascular disorders. The large sample size of this study ensured adequate statistical power to detect small sample-size associations, and to account for the effect of many potential confounders. Third, the multi-cohort study used a relatively novel statistical procedure, the counterfactual mediation method, which provides a less biased assessment of the contribution of a given mediator [22]. Fourth, we applied a life-course approach in this thesis, which allowed us to account for the effect of socioeconomic circumstances across different life phases on intermediate mechanisms and health-related outcomes in later life [23]. Finally, the major strength of the DNA methylation analysis was the genome-wide approach, which examined life-course SEP-induced differential methylation across the *entire* genome (hence using an exploratory hypothesis-generating approach), potentially unraveling unknown biological processes of the social embedding.

However, these studies also have important limitations to acknowledge. First, the articles included in the systematic review displayed important differences in terms of sociodemographic characteristics of study participants, study periods, potential confounders,

and the assessment methods of SEP, health behaviors, and health-related outcomes, which considerably limited between-study comparisons and precluded the statistical integration of results through a meta-analysis [24, 25]. An additional limitation related to the systematic review is the use of the difference method to estimate the contribution of health behaviors across included articles, as this approach does not account for all the possible confounding and interactions between the exposure, the mediators, and the outcomes, eventually yielding biased mediation estimates [22].

Another major limitation is related to the overall cross-sectional nature of the studies presented in chapters 2 and 3, which prevents establishing a cause-to-effect relationship and allows for the possibility of reverse causality. In particular, former research has reported that the relation between sleep duration and cardiovascular disorders was not exclusively unidirectional, whereby pre-existing health problems may also lead to sleep disturbances in some contexts [12]. Nevertheless, we managed to address this issue by using indicators of SEP in early-life, and by performing a longitudinal analysis in the Whitehall II study, showing temporal cause-to-effect relationships between low SEP and short sleep duration, between low SEP and a higher incidence of coronary heart disease, and between short sleep duration and an increased CHD risk. Moreover, while we identified a large number of SEP-related CpG markers involved in inflammatory pathways in chapter 3, we could not determine whether these CpGs lead to abnormal inflammation, or if they occurred as a consequence of pre-existing inflammatory processes [26].

The use of self-reported data in chapters 2 and 3 represents another important limitation in this thesis. In the multi-cohort analysis examining the contribution of sleep duration, the majority of cohorts used self-reported data on SEP in adulthood and cardiovascular disorders, whereas the remaining factors (early-life SEP, sleep duration, confounding factors) were

exclusively self-reported by study participants. Such an extensive use of self-reported data may represent an important issue in terms of recall bias and other types of systematic errors, yielding distorted associations between SEP, sleep duration and cardiovascular disorders [27, 28]. Moreover, we also observed that none of the SEP indicators in childhood were associated with a differential methylation of CpG markers, which may be related to a biased recall of socioeconomic circumstances in early life, as suggested by former research [15].

Finally, the small sample size used in the epigenome-wide analysis represents a further limitation, as it restricts the ability to detect small effect-size associations occurring between self-reported SEP and differential CpG methylation [26].

Conclusion and future perspectives

The studies included in this thesis have provided comprehensive answers and a novel insight on the role of intermediate mechanisms and biological processes underlying the life-course socioeconomic gradient in cardiometabolic disorders. However, this thesis has also yielded several important questions.

First, even though the *individual* role of intermediate mechanisms such as health behaviors, psychosocial stressors, sleep, and other factors, has been examined, evidence is lacking for the *overall* contribution of these factors to the life-course socioeconomic gradient in cardiometabolic disorders. One of the main reasons for this gap is the lack of understanding of the causal relations and interactions existing between these intermediate factors, which need to be specifically defined and accounted for in statistical models assessing the contribution of multiple mediators [29]. Moreover, a global understanding of the socioeconomic differences in cardiometabolic disorders also calls for a more systematic use of the life-course approach, whereby the role of socioeconomic circumstances across

different life phases shall be examined in the light of the causal models defined by life-course epidemiology (accumulation, critical periods, and chains of risk models) [23]. Nevertheless, conducting research combining the life-course approach along with the contribution of multiple mediators represents a major challenge in practice, as the statistical and causal inference tools allowing these analyses generally require strong assumptions, and have not been fully developed to this date [29, 30].

Furthermore, while we found that most of the SEP-related CpG markers are located within genes involved in inflammation, the exact exposures driving differential DNA methylation, and the physiological consequences of these alterations are unknown [26]. Former investigations conducted in animal models have suggested that an inferior rank in the social hierarchy affects the methylation and the expression of stress-related and pro-inflammatory genes, which in turn "prepare" the body to threat and potential injuries, but have detrimental effects on cardiovascular outcomes on the long term [31-33]. However, it remains to be determined to what extent such biological processes operate in response to adverse socioeconomic circumstances in humans, what are the exact exposures (i.e. psychosocial factors, environmental exposures) and the physiological mechanisms driving the differential DNA methylation, and how these alterations eventually translate into a higher cardiometabolic disease risk in later life. Related to the above, future epidemiologic research shall also aim for a more integrative approach of the SEP-related biological pathways (i.e. amygdala activity, HPA-axis, DNA methylation, inflammation), examining the mutual interactions between these processes, and their global role in the occurrence of cardiometabolic disorders [34].

Implications for public health

In addition to a more comprehensive understanding of the mechanisms underlying the socioeconomic gradient in cardiometabolic disorders, our findings may also have important implications for public health policies aimed at reducing these inequalities.

The results obtained in our systematic review showed a major contribution of health behaviors in shaping the relation between socioeconomic factors and cardiometabolic disorders. Throughout the second half of the twentieth century, the prevalence of cardiometabolic disorders and unhealthy behaviors (i.e. smoking, physical inactivity, consumption of highly-processed foods) has been steadily decreasing in the higher socioeconomic groups, while simultaneously increasing in more disadvantaged people in high-income countries [4, 35, 36]. As addressed in the introduction, this transition resulted from major economic development occurring in the post-war Western societies, whereby products such as tobacco, sugar, or processed foods became widely available, but also due to social phenomena, including a better response to public health messages by the higher socioeconomic groups [4, 37, 38]. Additionally, other factors further contributed to a greater prevalence of unhealthy behaviors in the lower socioeconomic groups, such as deprived neighborhoods offering few or no opportunities for a healthy lifestyle [35, 39]. Overall, these observations suggest that smoking, inadequate diet, physical inactivity, or other unhealthy "behaviors" are widely driven by the circumstances in which people are born, grow, live, and die, rather than entirely resulting from personal choices [35, 37]. In order to reduce the burden of cardiometabolic disorders, structural rather than agentic public health policies targeting unhealthy behaviors shall be implemented [37]. Indeed, former research has shown that agentic interventions encouraging individuals to adopt a healthier life-style were generally more efficient in the higher socioeconomic groups, due to greater resources,

knowledge or discernment capacity, eventually leading to an even higher socioeconomic gradient in cardiometabolic disorders [37, 40, 41]. On the other hand, structural policies such as raising tobacco prices, smoking bans in public spaces, trans-fat bans, and taxation of soft drinks, were generally found to benefit *all* socioeconomic groups, and particularly the more disadvantaged ones, further reducing health inequalities [41-44].

In addition to health behaviors, this thesis has pointed out towards the role of sleep as another important intermediate factor of the socioeconomic gradient in cardiometabolic disorders. Sleep is an essential recovery and restauration process, and sleep deprivation and other sleep-related problems have been related to major cardiometabolic disorders [10]. As part of the economic, social, and cultural changes that took place in the West during the twentieth century, the average sleep duration has been steadily decreasing, with socioeconomically disadvantaged individuals being particularly affected [9, 45, 46]. Consequently, to further reduce the burden and the socioeconomic differences in cardiometabolic disorders, structural policies shall aim at addressing socially patterned sleep disturbing factors, such as shift work, nighttime noise, or light pollution, which were previously associated with adverse cardiometabolic outcomes [45-50].

Furthermore, in the last part of this thesis, we observed that poor socioeconomic circumstances in adulthood were associated with a differential methylation of inflammation-related CpG markers. While aberrant inflammation was previously related to an increased cardiometabolic risk, further investigations are needed to identify and address the socially patterned exposures (i.e. psychosocial stressors, environmental factors) driving the differential methylation of the SEP-related markers.

Finally, the most important aspect in reducing the socioeconomic gradient in cardiometabolic disorders shall consist in eliminating the socioeconomic disadvantage itself. Even if the role

of most intermediate mechanism is eventually characterized, the fundamental causes of socioeconomic inequalities in health-related outcomes would still need to be fully understood and addressed directly [35, 51]. Former research in public health has thus shown that policies aimed at improving different aspects of the SEP, such as conditional cash transfers, the introduction of a universal basic income, or the promotion of social mobility through education, lead to an overall improvement of health [35, 37, 52-55]. Nevertheless, while eliminating socioeconomic inequalities would require extensive social, economic, and political effort at every level of society, a further characterization of the underlying mechanisms of the socioeconomic gradient in health-related outcomes remains absolutely essential for implementing effective, evidence-based public health policies addressing health inequalities.

References

1. Stringhini, S., et al., *Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts.* PLoS Med, 2011. **8**(2): p. e1000419.
2. Omran, A.R., *The epidemiologic transition: a theory of the epidemiology of population change.* The Milbank Quarterly, 2005. **83**(4): p. 731-757.
3. Lopez, A.D., N.E. Collishaw, and T. Piha, *A descriptive model of the cigarette epidemic in developed countries.* Tobacco control, 1994. **3**(3): p. 242.
4. Wilkinson, R.G., *The epidemiological transition: from material scarcity to social disadvantage?* Daedalus, 1994: p. 61-77.
5. Shamshirgaran, S.M., et al., *Independent roles of country of birth and socioeconomic status in the occurrence of type 2 diabetes.* BMC public health, 2013. **13**(1): p. 1.
6. Dinwiddie, G.Y., R.E. Zambrana, and M.A. Garza, *Exploring risk factors in Latino cardiovascular disease: the role of education, nativity, and gender.* American journal of public health, 2014. **104**(9): p. 1742-1750.
7. Stringhini, S., et al., *Association of socioeconomic position with health behaviors and mortality.* Jama, 2010. **303**(12): p. 1159-1166.
8. Ertel, K.A., L.F. Berkman, and O.M. Buxton, *Socioeconomic status, occupational characteristics, and sleep duration in African/Caribbean immigrants and US White health care workers.* Sleep, 2011. **34**(4): p. 509.
9. Jarrin, D.C., et al., *Objective and subjective socioeconomic gradients exist for sleep quality, sleep latency, sleep duration, weekend oversleep, and daytime sleepiness in adults.* Behavioral sleep medicine, 2013. **11**(2): p. 144-158.
10. Mullington, J.M., et al., *Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation.* Progress in cardiovascular diseases, 2009. **51**(4): p. 294-302.
11. Tomfohr, L.M., S. Ancoli-Israel, and J.E. Dimsdale, *Childhood socioeconomic status and race are associated with adult sleep.* Behavioral sleep medicine, 2010. **8**(4): p. 219-230.
12. Patel, S.R., et al., *Correlates of long sleep duration.* Sleep, 2006. **29**(7): p. 881.
13. Stringhini, S., et al., *Life-course socioeconomic status and DNA methylation of genes regulating inflammation.* International journal of epidemiology, 2015. **44**(4): p. 1320-1330.
14. Needham, B.L., et al., *Life course socioeconomic status and DNA methylation in genes related to stress reactivity and inflammation: The multi-ethnic study of atherosclerosis.* Epigenetics, 2015. **10**(10): p. 958-969.
15. Batty, G.D., et al., *Accuracy of adults' recall of childhood social class: findings from the Aberdeen children of the 1950s study.* Journal of Epidemiology & Community Health, 2005. **59**(10): p. 898-903.
16. Fraga, S., et al., *Association of socioeconomic status with inflammatory markers: a two cohort comparison.* Preventive medicine, 2015. **71**: p. 12-19.
17. Hansson, G.K., *Inflammation, atherosclerosis, and coronary artery disease.* New England Journal of Medicine, 2005. **352**(16): p. 1685-1695.
18. Stringhini, S., et al., *Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study.* PLoS Med, 2013. **10**(7): p. e1001479.
19. Dunn, B.K., et al., *Health disparities in breast cancer: biology meets socioeconomic status.* Breast cancer research and treatment, 2010. **121**(2): p. 281-292.
20. Welch, V., et al., *Guidelines and Guidance-PRISMA-Equity 2012 Extension: Reporting Guidelines for Systematic Reviews with a Focus on Health Equity.* PLoS Medicine, 2012. **9**(10): p. 1487.
21. Wright, R.W., et al., *How to write a systematic review.* Clinical Orthopaedics and Related Research (1976-2007), 2007. **455**: p. 23-29.

22. Valeri, L. and T.J. VanderWeele, *Mediation analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros.* Psychological methods, 2013. **18**(2): p. 137.
23. Kuh, D., et al., *Life course epidemiology.* Journal of epidemiology and community health, 2003. **57**(10): p. 778.
24. Higgins, J.P. and S.G. Thompson, *Quantifying heterogeneity in a meta-analysis.* Statistics in medicine, 2002. **21**(11): p. 1539-1558.
25. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* Bmj, 2003. **327**(7414): p. 557-560.
26. Heijmans, B.T. and J. Mill, *Commentary: The seven plagues of epigenetic epidemiology.* International journal of epidemiology, 2012. **41**(1): p. 74-78.
27. Coughlin, S.S., *Recall bias in epidemiologic studies.* Journal of clinical epidemiology, 1990. **43**(1): p. 87-91.
28. Kuper, H. and M. Marmot, *Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study.* Journal of Epidemiology & Community Health, 2003. **57**(2): p. 147-153.
29. VanderWeele, T. and S. Vansteelandt, *Mediation analysis with multiple mediators.* Epidemiologic methods, 2014. **2**(1): p. 95-115.
30. VanderWeele, T.J. and E.J. Tchetgen Tchetgen, *Mediation analysis with time varying exposures and mediators.* Journal of the Royal Statistical Society: Series B (Statistical Methodology), 2017. **79**(3): p. 917-938.
31. Tung, J., et al., *Social environment is associated with gene regulatory variation in the rhesus macaque immune system.* Proceedings of the National Academy of Sciences, 2012. **109**(17): p. 6490-6495.
32. Sapolsky, R.M., *The influence of social hierarchy on primate health.* Science, 2005. **308**(5722): p. 648-652.
33. Kinnally, E., *Epigenetic plasticity following early stress predicts long-term health outcomes in rhesus macaques.* American journal of physical anthropology, 2014. **155**(2): p. 192-199.
34. Wolfe, B., W. Evans, and T.E. Seeman, *Biological Consequences of Socioeconomic Inequalities, The*. 2012: Russell Sage Foundation.
35. Marmot, M.G. and R.G. Wilkinson, *Social Determinants of Health*. 1999: Oxford University Press.
36. Marmot, M.G., et al., *Changing social-class distribution of heart disease.* Br Med J, 1978. **2**(6145): p. 1109-1112.
37. Marmot, M., *The health gap: the challenge of an unequal world*. 2015: Bloomsbury Publishing.
38. Darmon, N. and A. Drewnowski, *Does social class predict diet quality?* The American journal of clinical nutrition, 2008. **87**(5): p. 1107-1117.
39. Walker, R.E., C.R. Keane, and J.G. Burke, *Disparities and access to healthy food in the United States: A review of food deserts literature.* Health & place, 2010. **16**(5): p. 876-884.
40. Beydoun, M.A. and Y. Wang, *Do nutrition knowledge and beliefs modify the association of socio-economic factors and diet quality among US adults?* Preventive medicine, 2008. **46**(2): p. 145-153.
41. Hiscock, R., et al., *Socioeconomic status and smoking: a review.* Annals of the New York Academy of Sciences, 2012. **1248**(1): p. 107-123.
42. Backholer, K., et al., *A framework for evaluating the impact of obesity prevention strategies on socioeconomic inequalities in weight.* American journal of public health, 2014. **104**(10): p. e43-e50.
43. Fletcher, J.M., D. Frisvold, and N. Tefft, *Can soft drink taxes reduce population weight?* Contemporary economic policy, 2010. **28**(1): p. 23-35.
44. Turrell, G. and S. Vandevijvere, *Socio-economic inequalities in diet and body weight: evidence, causes and intervention options.* Public health nutrition, 2015. **18**(5): p. 759-763.

45. Knauth, P., et al., *Duration of sleep depending on the type of shift work.* International Archives of Occupational and Environmental Health, 1980. **46**(2): p. 167-177.
46. Ferrie, J.E., et al., *Sleep epidemiology—a rapidly growing field.* International Journal of Epidemiology, 2011. **40**(6): p. 1431-1437.
47. Dragano, N., et al., *Traffic exposure and subclinical cardiovascular disease: is the association modified by socioeconomic characteristics of individuals and neighbourhoods? Results from a multilevel study in an urban region.* Occupational and environmental medicine, 2009. **66**(9): p. 628-635.
48. Joost, S., et al., *Spatial clusters of daytime sleepiness and association with nighttime noise levels in a Swiss general population (GeoHypnoLaus).* International journal of hygiene and environmental health, 2018. **221**(6): p. 951-957.
49. Stringhini, S., et al., *Association of socioeconomic status with sleep disturbances in the Swiss population-based CoLaus study.* Sleep medicine, 2015. **16**(4): p. 469-476.
50. Fonken, L.K., et al., *Light at night increases body mass by shifting the time of food intake.* Proceedings of the National Academy of Sciences, 2010. **107**(43): p. 18664-18669.
51. Rose, G., *Sick individuals and sick populations.* International journal of epidemiology, 2001. **30**(3): p. 427-432.
52. Rawlings, L.B. and G.M. Rubio, *Evaluating the impact of conditional cash transfer programs.* The World Bank Research Observer, 2005. **20**(1): p. 29-55.
53. Painter, A., *A universal basic income: the answer to poverty, insecurity, and health inequality?* 2016, British Medical Journal Publishing Group.
54. Johnson-Lawrence, V., G. Kaplan, and S. Galea, *Socioeconomic mobility in adulthood and cardiovascular disease mortality.* Annals of epidemiology, 2013. **23**(4): p. 167-171.
55. Milburn, A., *University challenge: How higher education can advance social mobility.* London: Cabinet Office, 2012.