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FULL RESEARCH PAPER
Risk prediction/assessment & stratification

Comparison of the European and US guidelines for lipid-lowering therapy in primary prevention of cardiovascular disease

Benoît Delabays [1]*†, Roxane de La Harpe [1†], Peter Vollenweider [1], Stephane Fournier[2], Olivier Müller [2], Davide Strambo [3], Ian Graham [4], Frank L.J. Visseren[5], David Nanchen[6], Pedro Marques-Vidal[1], and Julien Vaucher [1]

[1]Department of Medicine, Division of Internal Medicine, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, Lausanne 1011, Switzerland; [2]Heart and Vessel Department, Division of Cardiology, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, Lausanne 1011, Switzerland; [3]Department of Clinical Neurosciences, Division of Neurology, Lausanne University Hospital and University of Lausanne, Rue du Bugnon 46, Lausanne 1011, Switzerland; [4]School of Medicine, Trinity College Dublin, The University of Dublin, College Green, Dublin 2 D02 PN40, Ireland; [5]Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University, Heidelberglaan 100, Utrecht 3584 CX, Netherlands; and [6]Center for Primary Care and Public Health (Unisanté), University of Lausanne, Rue du Bugnon 44, Lausanne 1011, Switzerland

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Aims

Population-wide impacts of new guidelines in the primary prevention of atherosclerotic cardiovascular disease (ASCVD) should be explored in independent cohorts. Assess and compare the lipid-lowering therapy eligibility and predictive classification performance of 2016 and 2021 European Society of Cardiology (ESC), 2019 American Heart Association/American College of Cardiology (AHA/ACC), and 2022 US Preventive Services Task Force (USPSTF) guidelines.

Methods and results

Participants from the CoLaus|PsyCoLaus study, without ASCVD and not taking lipid-lowering therapy at baseline. Derivation of 10-year risk for ASCVD using Systematic COronary Risk Evaluation (SCORE1), SCORE2 [including SCORE2-Older Persons (SCORE2-OP)], and pooled cohort equation. Computation of the number of people eligible for lipid-lowering therapy based on each guideline and assessment of discrimination and calibration metrics of the risk models using first incident ASCVD as an outcome. Among 4,092 individuals, 158 (3.9%) experienced an incident ASCVD during a median follow-up of 9 years (interquartile range, 1.1). Lipid-lowering therapy was recommended or considered in 40.2% (95% confidence interval, 38.2–42.2), 26.4% (24.6–28.2), 28.6% (26.7–30.5), and 22.6% (20.9–24.4) of women and in 62.1% (59.8–64.3), 58.7% (56.4–61.0), 52.6% (50.3–54.9), and 48.4% (46.1–50.7) of men according to the 2016 ESC, 2021 ESC, 2019 AHA/ACC, and 2022 USPSTF guidelines, respectively. 43.3 and 46.7% of women facing an incident ASCVD were not eligible for lipid-lowering therapy at baseline according to the 2021 ESC and 2022 USPSTF, compared with 21.7 and 38.3% using the 2016 ESC and 2019 AHA/ACC, respectively.

Conclusion

Both the 2022 USPSTF and 2021 ESC guidelines particularly reduced lipid-lowering therapy eligibility in women. Nearly half of women who faced an incident ASCVD were not eligible for lipid-lowering therapy.

Lay summary

Question: Compared with previous European and US guidelines, what are the population-wide impacts of the 2021 European Society of Cardiology (ESC) and 2022 US Preventive Services Task Force (USPSTF) guidelines for primary cardiovascular prevention in terms of lipid-lowering therapy eligibility and risk classification performance?

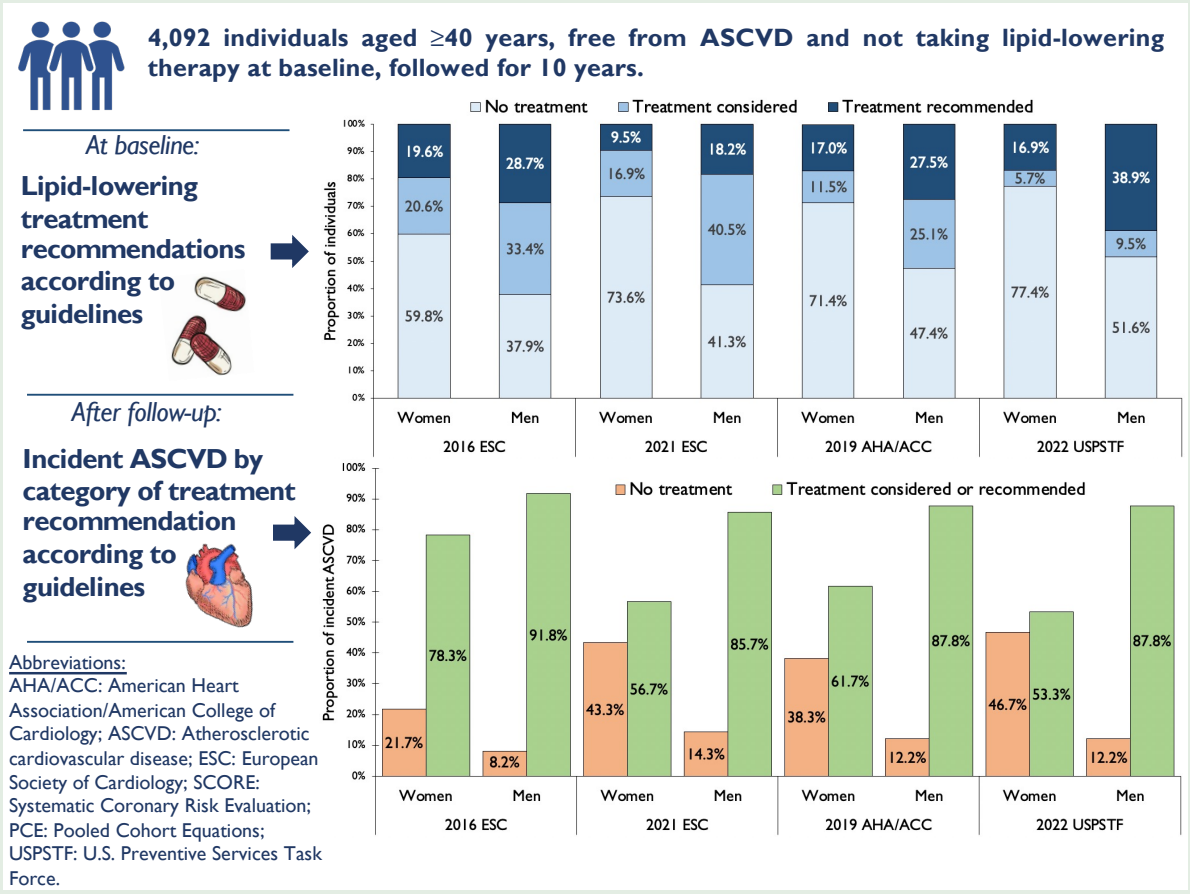
Key findings: In a population-based cohort study comprising 4069 adults free from cardiovascular disease and lipid-lowering treatment, the implementation of both guidelines resulted in a lower proportion of treatment-eligible individuals compared with the 2016 ESC and 2019 American Heart Association/American College of Cardiology guidelines, especially

* Corresponding author. Tel: +41 79 696 69 14, Fax: +41 21 314 80 37, Email: benoit.delabays@chuv.ch
† Co-first authors

among women. In women, nearly half of 10-year incident cardiovascular events occurred in those for whom a lipid-lowering therapy was not recommended.

Meanings: The 2021 ESC and 2022 USPSTF guidelines reduced overtreatment but did not improve the identification of individuals who will develop atherosclerotic cardiovascular disease. There is a need to better stratify the cardiovascular risk in women.

Graphical Abstract



Keywords Cardiovascular • Primary prevention • Guidelines • Risk score • Validation • Lipid-lowering therapy

Introduction

The US Preventive Services Task Force (USPSTF) published in August 2022 new recommendations for lipid-lowering therapy in adults 40 years or older without a history of known atherosclerotic cardiovascular disease (ASCVD) and who do not have signs and symptoms of ASCVD.[1] Likewise, the European Society of Cardiology (ESC) released in 2021 new guidelines for optimal cardiovascular prevention.[2] Both guidelines recommend assessing 10-year risk of ASCVD to guide lipid-lowering therapy. The ESC introduced novel prediction models, namely Systematic COronary Risk Evaluation 2 (SCORE2) and SCORE2-Older Persons (SCORE2-OP), using large individual participant data from numerous prospective cohorts and applicable to people aged 40–69 years or 70 years and older, respectively.[3,4] The previously recommended model in Europe was the SCORE1.[5] However, SCORE1 was derived from old cohorts and included only fatal cardiovascular outcomes, limiting its applicability to present European populations whose contemporary cardiovascular disease rates have changed and shifted towards a majority of non-fatal outcomes. The risk estimation model prevailing in North America since 2013 is the Pooled Cohort Equations (PCE).[6] This model is recommended by both the USPSTF[1] and the American Heart Association/American College of Cardiology (AHA/ACC) task force[7] that issued 2019 guidelines on primary cardiovascular prevention.

As different guidelines and prediction models can translate into substantial variations in the proportion of individuals at risk and thus eligible for lipid-lowering therapy, there exists a need to thoroughly determine the population-wide impact of the 2021 ESC and 2022 USPSTF guidelines (in comparison with previous recommendations or from other populations) and to ascertain the calibration of the corresponding prediction models. We thus compared previous (2016) and recent (2021) ESC guidelines as well as the 2019 AHA/ACC and 2022 USPSTF guidelines on cardiovascular prevention in individuals aged 40 and older. We first aimed to compare the proportion of individuals considered at risk

and thus eligible for lipid-lowering therapy across the four guidelines. Second, we collected 10-year incident ASCVD and assessed the discriminative and calibration performances of the three risk prediction models endorsed by these guidelines.

Methods

Study participants

The CoLaus|PsyCoLaus study is a population-based prospective cohort investigating clinical, psychological, genetic, and social determinants of cardiovascular disease.[8] Between 2003 and 2006, 6733 subjects (age range 35–75 years, 54% women) were recruited from a random sample of the population of the city of Lausanne (participation rate 41%) for baseline extensive phenotyping with clinical assessment, questionnaires on health and lifestyle, and blood sampling. Periodic resurveys of the whole cohort were conducted over an 18-year follow-up. Appropriate medical records of participants who declared an incident ASCVD and/or ASCVD-related procedure were prospectively collected, as well as information on the cause of death. Atherosclerotic cardiovascular disease and causes of death were independently adjudicated by cardiologists, neurologists, and internists. The complete procedure has been previously described.[9] The Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the CoLaus|PsyCoLaus study (project number PB_2018-00038, reference 239/09).

Inclusion criteria

Individuals aged more than 40 years and free from prevalent ASCVD from the cohort's first follow-up (2009–2012) were included, amounting to 5064 participants. Participants with previous ASCVD, lipid-lowering therapy, or missing data at baseline were excluded. We chose the first follow-up of CoLaus|PsyCoLaus as baseline for our analyses to derive our results from the most contemporaneous data and thus minimize secular bias in cardiovascular prevention.

Risk factor measurement

A set of questionnaires recorded information on demographic data, socioeconomic status, and several lifestyle factors, notably tobacco consumption (previous and current smoking status). Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic BP (DBP) ≥ 90 mmHg during the visit and/or presence of anti-hypertensive drug treatment. Low-density lipoprotein cholesterol (LDL-C) levels were calculated based on Sampson's equation.[10] Diabetes mellitus (DM) was defined as fasting plasma glucose ≥ 7.0 mmol/L and/or the presence of anti-diabetic treatment. Type 2 DM was defined in the case of diabetes without self-reported type 1 DM. A urine sample was collected for the assessment of creatinine and albumin, and the albumin-to-creatinine ratio was calculated. Microalbuminuria was defined as a value of albumin-to-creatinine ratio above 30 mg/g. The complete methodology of the CoLaus|PsyCoLaus study has been previously described.[8]

Cardiovascular guidelines, lipid-lowering therapy recommendations, risk prediction models, and outcomes

First, the four clinical guidelines were compared, namely the ESC 2016, ESC 2021, AHA/ACC 2019, and USPSTF 2022 guidelines.[1,2,7,11] Risk categories and lipid-lowering therapy recommendations were determined by the risk prediction models and criteria of the ESC,[2,11] ACC/AHA,[7] and USPSTF,[1] respectively, to reclassify individuals in higher categories of risk (see Supplementary material online, *Table S1* and *Figures S1–S4*). As lipid-lowering therapy can be considered in individuals at borderline risk according to the 2019 AHA/ACC guidelines, a sensitivity analysis was performed by including those individuals in the 'treatment considered' group. We also performed a sensitivity analysis with the 2022 USPSTF guidelines, by including people with a 10-year risk ≥5% with one or more ASCVD risk factors in the 'treatment considered' group.

Second, the three risk prediction models (cardiovascular risk scores) were compared, namely SCORE1, SCORE2 (including SCORE2-OP, for people aged >70 years), and PCE. The low-risk region recalibrated models of SCORE1, SCORE2, and SCORE2-OP were used.[3,4,9] Pooled Cohort Equation was recalibrated as previously proposed.[12] Scores were computed for each participant without medical conditions putting them at immediate very high cardiovascular risk, according to each guideline separately (see Supplementary material online, *Table S1*) and with follow-up data.

A common set of cardiovascular outcomes, namely ASCVD, was used for comparison purposes, as already performed[9,13,14] and recommended by the 2021 ESC and 2019 ACC/AHA guidelines on cardiovascular prevention.[2,7] Atherosclerotic cardiovascular disease comprised (i) fatal or non-fatal acute myocardial infarction, (ii) sudden cardiac death or cardiovascular death, and (iii) fatal and non-fatal ischaemic stroke (including transient ischaemic attack). The definition criteria of these endpoints in the CoLaus|PsyCoLaus study were previously reported.[9]

Statistical analysis

Baseline participants' characteristics were expressed as number (percentage) for categorical variables and as mean ± standard deviation (SD) for continuous variables, stratified by sex. Pearson's χ^2 (for categorical variables) or analysis of variance (for continuous variables) was used to evaluate differences in characteristics. According to each guideline separately, we determined the number of participants who were eligible for lipid-lowering therapy and the number of incident ASCVD in each risk group, according to guidelines and risk prediction models.

Discrimination was assessed with sensibility, specificity, positive and negative predictive values, and area under the receiver operating characteristic curve (AUROC), with corresponding 95% confidence intervals (CI), using incident ASCVD as the outcome. Scores were tested by dichotomizing the predicted risk as follows: low/intermediate (<5%) vs. high/very high categories of risk for SCORE1; low-moderate (<2.5 or <7.5% depending on age) vs. high/very high categories of risk for SCORE2; and low/borderline (<7.5%) vs. intermediate/high categories of risk for PCE. Calibration was assessed with the Brier score and the Hosmer–Lemeshow test. Calibration plots were generated using predicted outcome probabilities calculated with Cox prediction models and observed outcome probabilities calculated with the Kaplan–Meier estimates.[15] Model fit was assessed with Akaike's and Bayesian information criteria. All statistical analyses were conducted in Stata version 17 (StataCorp, College Station, TX, USA).

Results

Study population

A total of 4092 participants (mean age 56.1 years, 55.7% of women) were included in the analysis (see Supplementary material online, *Figure S5*). Baseline participants' characteristics overall and according to sex are presented in *Tables 1* and *S2*. Women were significantly older than men, but smoking, LDL-C level, hypertension, and DM were more prevalent in men. During a median follow-up time of 9 years [interquartile range (IQR), 1.1], 158 participants (3.9%) presented a first incident ASCVD, of which 18 (11.4%) were fatal and 60 (38%) occurred in women. A total of 352 (8.6%) participants were lost to follow-up.

Categories of risk distribution and lipid-lowering therapy eligibility

The distribution of individuals in categories of risk according to each guideline is presented in Supplementary material online, *Table S3*. According to the ESC 2016, ESC 2021, AHA/ACC 2019, and USPSTF 2022 guidelines, lipid-lowering therapy would be recommended or considered in 40.2% (95% CI: 38.2–42.2), 26.4% (95% CI: 24.6–28.2), 28.6% (95% CI: 26.7–30.5), and 22.6% (95% CI: 20.9–24.4) of women and in 62.1% (95% CI: 59.8–64.3), 58.7% (95% CI: 56.4–61.0), 52.6% (95% CI: 50.3–54.9), and 48.4 (95% CI: 46.1–50.7) of men, respectively (*Figure 1* and Supplementary material online, *Table S4*).

Among 158 people having developed an ASCVD, 43.3% of women and 14.3% of men were not eligible for lipid-lowering therapy at

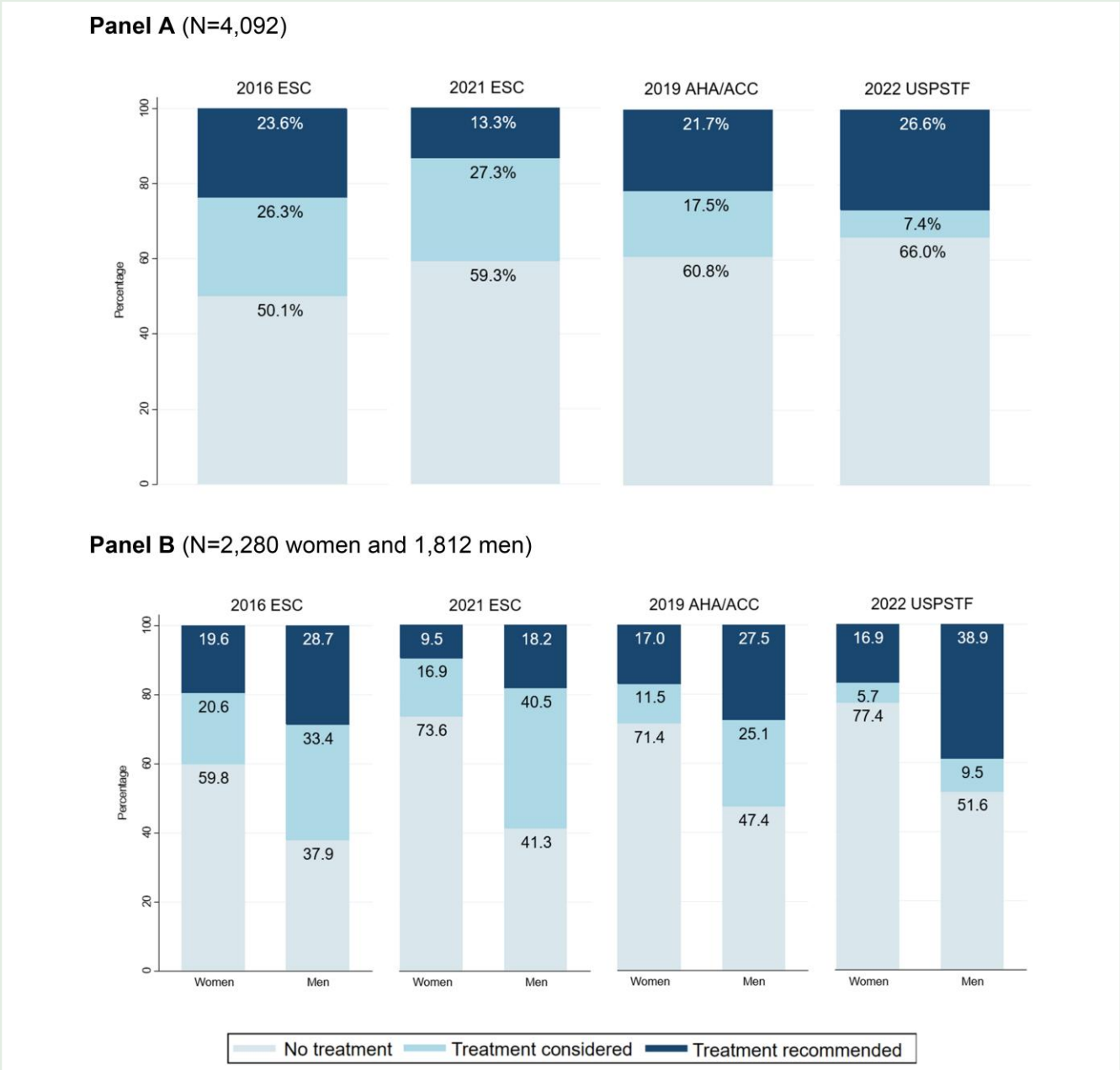


Figure 1 Lipid-lowering therapy recommendations in the participants at baseline based on the 2016 European Society of Cardiology, 2022 European Society of Cardiology, 2019 American Heart Association/American College of Cardiology, and 2022 US Preventive Services Task Force guidelines, overall (*A*) and by sex (*B*). The criteria to determine if lipid-lowering therapy was recommended or considered are presented in Supplementary material online, *Figures S1–S4*. ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; USPSTF, US Preventive Services Task Force.

baseline according to the ESC 2021. These proportions were similar when applying the 2022 USPSTF (46.7% of women and 12.2% of men) but differed substantially when using the 2016 ESC and 2019 AHA/ACC guidelines (21.7% and 38.3% of women and 8.2% and 12.2% of men, respectively). Only 9.1% of women and 16.4% of men not experiencing an ASCVD had treatment recommended at baseline with the 2021 ESC guidelines, figures lower than those of other algorithms (*Table 2*). 43.3% of women and 77.6% of men developing an ASCVD had a lipid-lowering therapy recommended with the 2022 USPSTF, compared with 45.0, 21.7, and 40.0% of women and 55.1, 40.8, and 53.1% of men using the 2016 ESC, 2021 ESC, and 2019 AHA/ACC, respectively (*Table 2*). Women [6.8% (5.0–9.0)] and men <50 years [48.0% (44.1–52.1)] were more often eligible for lipid-lowering therapy (i.e. treatment recommended or considered) using the 2021 ESC guidelines (*Figure 2*). Overall, 67% of the participants were similarly eligible for lipid-lowering therapy according to the 2021 ESC and 2019 AHA/ACC and 2022 USPSTF guidelines (see Supplementary material online, *Figure S6*).

Table 1 Participants' characteristics

n	All 4092	Women 2280	Men 1812	*P*-value
Age (years)	56.1 ± 10.2	56.8 ± 10.2	55.3 ± 10.0	<0.001
European	3975 (97.1)	2229 (97.8)	1746 (96.4)	0.007
Smokers	878 (21.5)	464 (20.4)	414 (22.9)	0.05
BMI (kg/m^2)	25.7 ± 4.4	25.1 ± 4.7	26.5 ± 3.9	<0.001
eGFR (CKD-EPI; mL/min/1.73 m^2)	84.3 ± 14.7	82.8 ± 14.7	86.1 ± 14.5	<0.001
Lipids (mmol/L)				
Total cholesterol	5.8 ± 1	5.9 ± 1	5.8 ± 1	<0.001
LDL-C	3.6 ± 0.9	3.5 ± 0.9	3.6 ± 0.9	<0.001
HDL-C	1.7 ± 0.5	1.8 ± 0.5	1.4 ± 0.4	<0.001
Triglycerides	1.3 ± 0.9	1.1 ± 0.6	1.5 ± 1.1	<0.001
Blood pressure (mmHg)				
Systolic	125 ± 18	121 ± 18	130 ± 16	<0.001
Diastolic	78 ± 11	76 ± 11	80 ± 11	<0.001
Hypertension	1362 (33.3)	645 (28.3)	717 (39.6)	<0.001
Anti-hypertensive treatment	710 (17.4)	369 (16.2)	341 (18.8)	0.03
Diabetes mellitus	288 (7.0)	94 (4.1)	194 (10.7)	<0.001
Platelet aggregation inhibitors	183 (4.5)	95 (4.2)	88 (4.9)	0.29
Incident ASCVD[a]	158 (3.9)	60 (2.6)	98 (5.1)	<0.001
Death from ASCVD as first event[b]	18 (0.4)	10 (0.4)	8 (0.4)	0.99
Total mortality from ASCVD[c]	26 (0.6)	13 (0.6)	13 (0.7)	0.56
Total mortality from other causes	218 (5.3)	97 (4.3)	121 (6.7)	0.001

Results are expressed as number of participants (column %), or as mean (±standard deviation). Percentages are expressed by row. *P*-values were derived using the Pearson χ^2 Student's *t*-test when appropriate.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration Equation; eGFR, estimated glomerular filtration rate; HDL-C high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]During a median follow-up time of 9 years (interquartile range, 1.1).
[b]Cases where the first incident atherosclerotic cardiovascular disease was fatal.
[c]Death from atherosclerotic cardiovascular disease during the study follow-up (without censoring after first incident atherosclerotic cardiovascular disease).

Table 2 Lipid-lowering therapy recommendations based on guidelines and incident atherosclerotic cardiovascular disease, by sex

	Incident atherosclerotic cardiovascular disease							
	2016 ESC		2021 ESC		2019 AHA/ACC		2022 USPSTF	
	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)
Men (*n* = 1637)	1539	98	1539	98	1539	98	1539	98
Treatment recommended	*420 (27.3)*	**54 (55.1)**	*253 (16.4)*	**40 (40.8)**	*399 (25.9)*	**52 (53.1)**	*571 (37.1)*	**76 (77.6)**
Treatment considered	508 (33.0)	36 (36.7)	617 (40.1)	44 (44.9)	382 (24.8)	34 (34.7)	145 (9.4)	10 (10.2)
No treatment	**611 (39.7)**	*8 (8.2)*	**669 (43.5)**	*14 (14.3)*	**758 (49.3)**	*12 (12.2)*	**823 (53.5)**	*12 (12.2)*
Women (*n* = 2103)	2043	60	2043	60	2043	60	2043	60
Treatment recommended	*393 (19.2)*	**27 (45.0)**	*185 (9.1)*	**13 (21.7)**	*339 (16.6)*	**24 (40.0)**	*340 (16.6)*	**26 (43.3)**
Treatment considered	421 (20.6)	20 (33.3)	340 (16.6)	21 (35.0)	237 (11.6)	13 (21.7)	116 (5.7)	6 (10.0)
No treatment	**1229 (60.2)**	*13 (21.7)*	**1518 (74.3)**	*26 (43.3)*	**1467 (71.8)**	*23 (38.3)*	**1587 (77.7)**	*28 (46.7)*

Incident atherosclerotic cardiovascular disease (*n* = 158) are shown in each category of treatment recommendation according to the different guidelines. *n* differs from the study sample at baseline because we excluded participants without follow-up ascertainment. Percentages are expressed by columns. Values in bold denote true positive individuals (i.e. treatment recommended in an individual developing an incident atherosclerotic cardiovascular disease), and italicized values denote false negative individuals (i.e. no treatment considered or recommended in an individual facing an incident atherosclerotic cardiovascular disease).
PCE, Pooled Cohort Equation; SCORE, Systematic COronary Risk Evaluation; USPSTF, US Preventive Services Task Force.

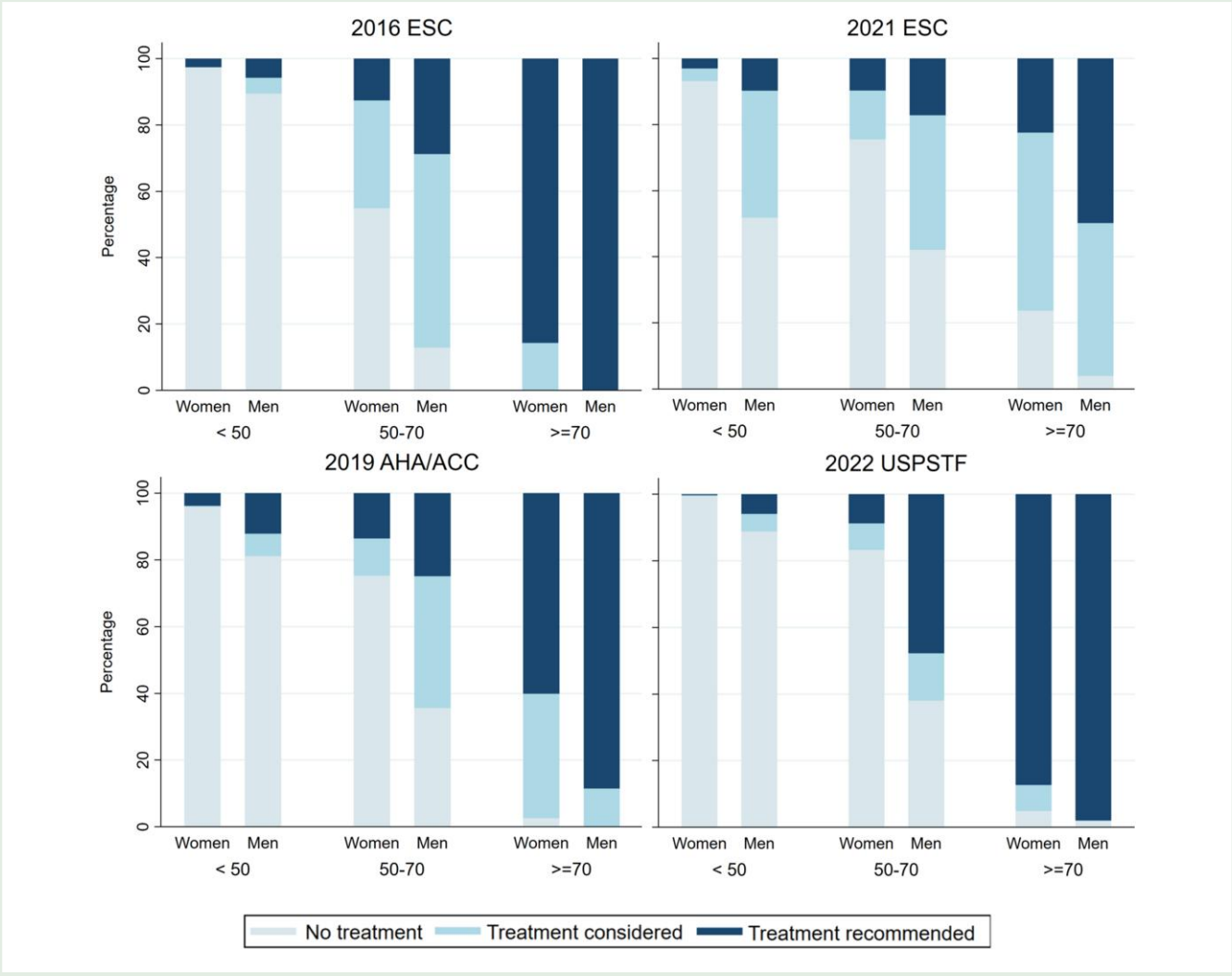


Figure 2 Lipid-lowering therapy recommendations based on the 2016 European Society of Cardiology, 2021 European Society of Cardiology, 2019 American Heart Association/American College of Cardiology, and 2022 US Preventive Services Task Force guidelines, stratified by age. $n = 2280$ women and 1812 men. The criteria to determine if lipid-lowering therapy was recommended or considered are presented in Supplementary material online, *Figures S1–S4*. ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; USPSTF, US Preventive Services Task Force.

Performance of the cardiovascular risk scores

The distribution of individuals in categories of risk according to each risk prediction model is presented in Supplementary material online, *Table S5*. The SCORE1 presented the highest specificity but a lower capacity to detect individuals at true cardiovascular risk compared with SCORE2 and PCE (sensitivity of 47.3% vs. 71.8% and 75.5%, respectively) (see Supplementary material online, *Table S6*). Discriminative performances of SCORE2 and PCE were higher than for SCORE1, with AUROC of 0.78 vs. 0.74, respectively ($P \leq 0.002$) (see Supplementary material online, *Table S6* and *Figure S7*). The SCORE2 and PCE had a lower capacity to detect individuals at true cardiovascular risk in women compared with men (see Supplementary material online, *Tables S7 and S8*).

The SCORE2 presented an overall good calibration but was the only risk model to under-predict risk in individuals at very high cardiovascular risk (*Figure 3*). The PCE constantly over-predicted risk, especially in high-risk categories. Calibration plots parting participants in deciles of risk are presented in Supplementary material online, *Figure S8*. The Hosmer–Lemeshow test was significant and the Brier score was equivalent among all risk models (see Supplementary material online, *Table S6*). Among people developing an ASCVD, there was a greater proportion of women compared with men who were not eligible for lipid-lowering-therapy across the three risk models (see Supplementary material online, *Table S9*).

Sensitivity analysis

Eligibility to lipid-lowering therapy, when considering treatment in individuals at borderline risk according to the AHA/ACC and USPSTF guidelines, is shown in Supplementary material online, *Table S10* and *Figure S9*. The proportion of women and men in whom a lipid-lowering therapy was not recommended but who faced an incident ASCVD was lower in this scenario (see Supplementary material online, *Table S11*).

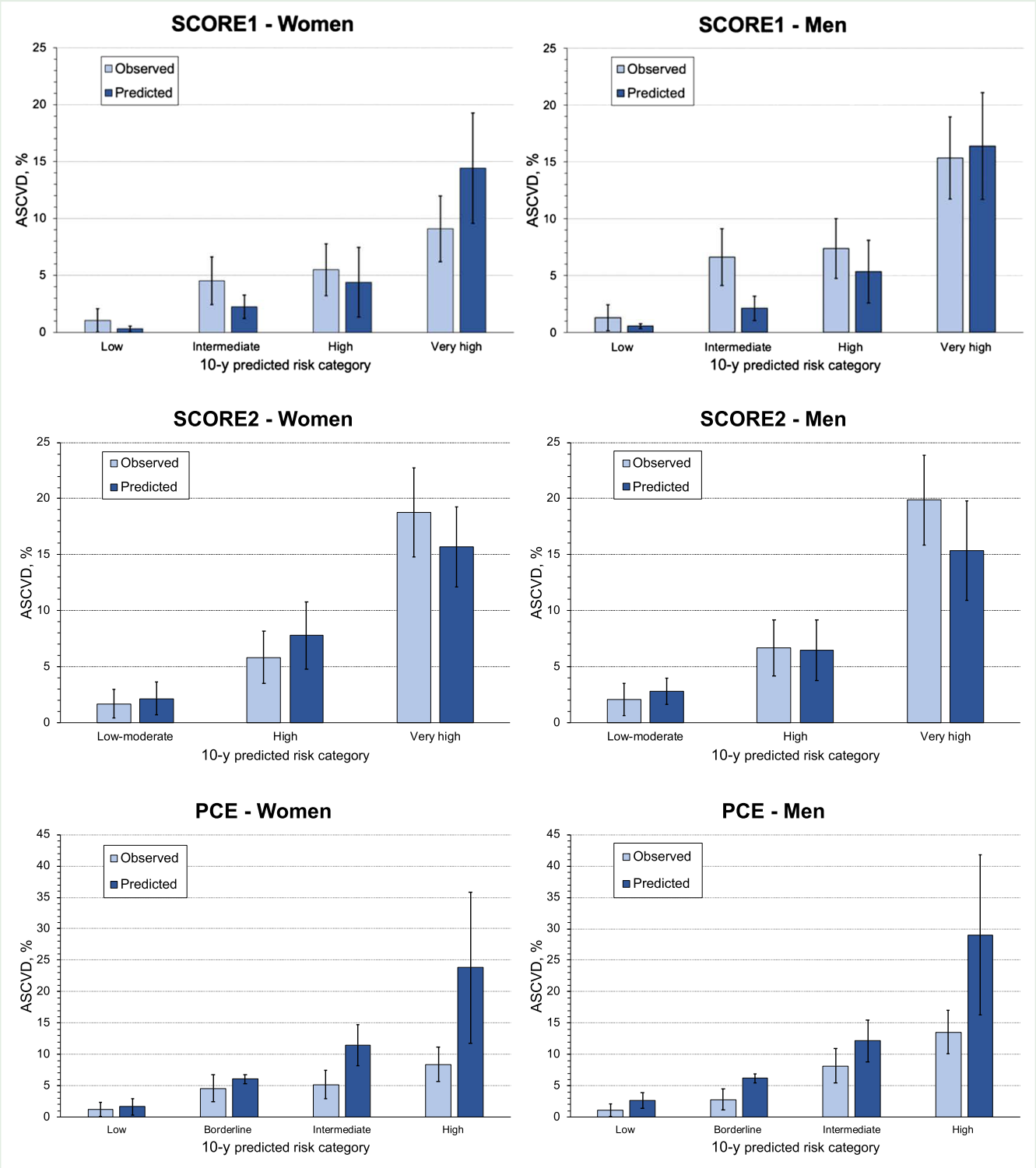


Figure 3 Observed vs. predicted risks compared by risk prediction models and by sex. Left-hand columns represent the observed risk of atherosclerotic cardiovascular disease; right-hand columns represent the predicted risk of atherosclerotic cardiovascular disease, by scores and by sex. Vertical bars indicate 95% confidence intervals. ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ESC, European Society of Cardiology; PCE, Pooled Cohort Equations; SCORE, Systematic COronary Risk Evaluation.

Discussion

Comparing previous (2016) and recent (2021) ESC, 2019 AHA/ACC, and 2022 USPSTF guidelines on primary cardiovascular prevention in a cohort of apparently healthy individuals, this study highlighted important discrepancies among the recommendations. First, the application of the 2021 ESC and the 2022 USPSTF guidelines translated into a lower proportion of individuals eligible for lipid-lowering therapy overall. The 2022 USPSTF guidelines resulted in a higher proportion of men with grade B recommendation for lipid-lowering therapy but a lower proportion of women qualifying for preventive treatment. Second, more women and men below 50 years would qualify for lipid-lowering therapy with the 2021 ESC guidelines but not with the 2022 USPSTF guidelines. Third, we observed that nearly half of women developing an ASCVD during the follow-up were not eligible for lipid-lowering therapy at baseline according to the 2021 ESC and 2022 USPSTF guidelines. The SCORE2 and PCE demonstrated good and comparable discriminative metrics, higher than SCORE1.

The present study should be interpreted in conjunction with the recent findings of Mortensen *et al.*,[16] who used data from 66 909 white individuals from the Copenhagen General Population Study. They compared lipid-lowering therapy eligibility for primary prevention of cardiovascular disease according to the 2021 ESC guidelines with other international guidelines. It is noteworthy that SCORE2-OP was not used due to the age range of participants (40–69 years), results were not systematically stratified by sex, and the 2022 USPSTF guidelines were not tested. Only 4% of the individuals qualified for primary prevention class I recommendations for lipid-lowering treatment, compared with 34% for the 2019 AHA/ACC and 20% for the 2019 ESC/European Atherosclerotic Society (EAS) guidelines.[17] The present data are characterized by a similar trend but an overall higher proportion of individuals qualifying for lipid-lowering therapy because older participants were included. As suggested by Navar *et al.*,[18] the dramatic drop in lipid-lowering therapy eligibility with new ESC guidelines can, first, be due to the influence of regional ASCVD burden on a risk prediction model which can negatively impact individual predicted risk. For example, the higher a country has decreased its ASCVD burden (mainly through lipid-lowering therapy implementation), the lower lipid-lowering therapies will be recommended by a score deriving risk estimates based on regional ASCVD burden. Second, the thresholds for treatment by age, sex, and region might play a role.[16] Therefore, primary prevention of cardiovascular disease would probably take advantage by focusing on a 'benefit' approach rather than a risk approach. As risk scores are highly influenced by age and derived using ASCVD as an outcome, lipid-lowering therapy recommendations might not capture the true risk stemming from lipid-mediated atherosclerosis.[19] A long-term benefit approach (estimating lipid-lowering therapy benefit through the level of cholesterol that should be lowered to mitigate a person's lifetime ASCVD risk) might be preferable, especially among young individuals who adopt preventive measures.[20,21] A positive finding of the present study is that the 2021 ESC guidelines better discriminate young individuals, male or female, in the various risk categories compared with previous ESC, 2019 AHA/ACC, and 2022 USPSTF guidelines. Thus, age-specific risk thresholds proposed by the 2021 ESC guidelines do not seem to negatively influence lipid-lowering therapy eligibility in young individuals.

Kavousi *et al.*[22] previously showed in a European cohort that the application of the 2013 AHA/ACC guidelines resulted in overtreatment in both sexes. In the present study, a substantially lower proportion of individuals were eligible for lipid-lowering therapy according to the 2021 ESC and 2022 USPSTF guidelines. Although this represents a positive development to avoid harmful consequences of overtreatment, the risk of missing an individual who will develop ASCVD remains a concern. A recent French study reported that one-third of individuals admitted for a first ST-segment elevation myocardial infarction would not have been eligible for lipid-lowering therapy based on the 2021 ESC criteria.[23] Our findings show that ~25% of ASCVD occur in individuals at low risk according to the 2021 ESC and 2022 USPSTF guidelines.

Women are particularly at risk for misclassification, irrespective of the guidelines. Both SCORE2 and PCE had a lower sensitivity to predict ASCVD in women. There exists a high burden of ASCVD in women (one in three die from ASCVD in the USA), and sex-specific factors (such as premature menopause or polycystic ovarian syndrome) have been recognized to influence ASCVD occurrence and progression.[24] Although women experiencing adverse pregnancy outcomes (e.g. preterm birth or gestational DM) had a two-fold increased risk of ASCVD, risk prediction models enhanced with these risk factors did not show higher predictive performances.[24] This suggests that we should integrate other risk-enhancing factors, possibly sex-specific, to improve risk stratification in certain groups of the population [e.g. familial history, coronary artery calcium score, polygenic risk scores, hormonal status, or lipoprotein(a)].[25,26]

Strengths and limitations

The present study, based on contemporaneous and independent data, helps to precise the performance of current guidelines on cardiovascular prevention and allows independent replication of previous findings.[16,27] In particular, well-characterized individuals and a meticulous collection of ASCVD allow for deriving robust conclusions. Moreover, the present analysis shows results stratified by age and sex, with class I and II (or grades B and C) recommendations for lipid-lowering therapy, which have not been presented yet.

A first limitation is that, due to the observational design of the study, we were not able to integrate any medical intervention that could have influenced ASCVD development during the follow-up, notably lipid-lowering therapy initiation. However, previous analyses suggested that longitudinal information on lipid-lowering therapy initiation provides only limited clinical benefit.[28] Second, we did not account for cardiovascular risk modifiers (such as coronary calcium scoring, which was not available in our cohort) and comorbidities (such as cancer or inflammatory disease) that may affect clinicians' decisions whether initiating or not a lipid-lowering therapy. Moreover, data on medical conditions putting diabetic individuals at higher cardiovascular risk according to the 2021 ESC guidelines, such as retinopathy and neuropathy,[2] were not available for analysis. Altogether, this could have minimized the number of individuals eligible for lipid-lowering therapy. Third, one should acknowledge the low precision of the calibration results due to the limited power of the sample size and hence the relativity of the determined differences between the risk models. We did not perform a comparison using SCORE1-specific outcomes (i.e. fatal ASCVD only), but we previously reported that the discrimination and calibration results were not significantly affected by the use of both fatal and non-fatal ASCVD as an outcome.[9] Finally, as participants in the present study were predominantly white Europeans, our results should not be extrapolated to other ethnic populations.

Conclusion

In comparison with the 2016 ESC and 2019 AHA/ACC guidelines, implementation of the 2021 ESC and 2022 USPSTF guidelines on cardiovascular prevention would result in an overall lower proportion of individuals eligible for lipid-lowering therapy. Importantly, the 2021 ESC and 2022 USTPF guidelines particularly reduced lipid-lowering therapy eligibility among women, including those being at true cardiovascular risk.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

B.D. and R.d.L.H. contributed equally to all parts of this work, performed statistical analysis, interpreted the results, and drafted the manuscript. D.N., P.M.-V., and J.V. contributed to the conception and design of the work and critically revised the manuscript. S.F., O.M., D.S., P.V., I.G., F.L.J.V., and P.M.-V. contributed to the acquisition, analysis, or interpretation of data and revised the manuscript for important intellectual content. J.V. had full access to the data and is the guarantor of the study. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interest: None declared.

Data availability

Non-identifiable, individual-level data are available for interested researchers, who meet the criteria for access to confidential data sharing, from the CoLaus Datacenter (CHUV, Lausanne, Switzerland). Instructions for gaining access to the CoLaus data used in this study are available at https://www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

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