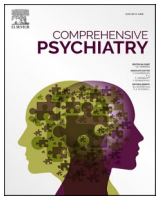
Comprehensive Psychiatry 129 (2024) 152442

Contents lists available at ScienceDirect

Comprehensive Psychiatry

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



Subtypes of major depressive disorders and objectively measured physical activity and sedentary behaviors in the community

Maulde Rovero [a], Martin Preisig [b], Pedro Marques-Vidal [c], Marie-Pierre F. Strippoli [b], Peter Vollenweider [c], Julien Vaucher [c,d], Alexandre Berney [e], Kathleen R. Merikangas [f], Caroline L. Vandeleur [b,*,1], Jennifer Glaus [g,1]

[a] Faculty of Medicine, University of Zurich, Switzerland
[b] Center for Research in Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Switzerland
[c] Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Switzerland
[d] Department of Medicine and Specialties, Internal Medicine, Fribourg Hospital and University of Fribourg, Switzerland
[e] Department of Psychiatry, Psychiatric Liaison Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[f] Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA
[g] Division of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Switzerland

ARTICLE INFO

Keywords:
Major depressive disorder subtypes
physical activity
sedentary behavior
actigraphy
psychiatric comorbidity
cardio-vascular risk factors

ABSTRACT

Background: Lack of physical activity (PA) and high sedentary behavior (SB) may enhance mental health problems, including depression, and are associated with increased mortality. Aside from a large body of research on major depressive disorder (MDD) assessed as an entity and either PA or SB, few studies have examined associations among subtypes of MDD and both PA and SB simultaneously derived from wrist-worn accelerometers. Accordingly, our aim was to explore the associations among MDD subtypes (atypical, melancholic, combined atypical-melancholic and unspecified) and four actigraphy-derived behaviors combining the levels of PA and SB.
Methods: The sample stemmed from CoLaus|PsyCoLaus, a population-based cohort study, consisting of 2375 participants (55.1% women; mean age: 62.4 years) who wore an accelerometer for 14 days after a physical exam and subsequently completed a semi-structured psychiatric interview. Activity behaviors were defined according to the combination of the levels of moderate-to-vigorous intensity PA and SB. Associations of remitted MDD subtypes, current MDD and physical inactivity behaviors were assessed using multinomial logistic regression, adjusted for socio-demographic characteristics, a history of anxiety, alcohol and drug use disorders and cardiovascular risk factors.
Results: In the fully adjusted model, participants with the remitted combined atypical-melancholic subtype had a higher risk of being more physically inactive.
Conclusions: Our findings suggest that low PA and high SB are not restricted to the duration of depressive episodes in people with atypical and melancholic episodes. The lack of PA and high SB in this group of depressive patients exposes them to an additional long-term cardiovascular risk and measures to increase PA may be particularly fruitful in this MDD subgroup.

1. Introduction

Major Depressive disorder (MDD) is a highly prevalent psychiatric disorder [1,2] and a burdensome condition in Western societies [3]. There is a large body of cross-sectional but also prospective research on the association between MDD and sedentary behaviors (SB) [4], which is a well-established cardiovascular risk factor (CVRF) [5] [6] associated with increased mortality [7]. In contrast, physical exercise has been shown to be associated with improved health [8]. Although SB and moderate to vigorous physical activity (MVPA) share a weak inverse relationship, an individual can have high levels of physical activity (PA) and still large amounts of sedentary time across a day [9]. The bulk of

* Corresponding author at: Center for Research in Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Route de Cery 25, CH-1008 Prilly, Switzerland.
E-mail address: Caroline.Vandeleur@chuv.ch (C.L. Vandeleur).
[1] Shared senior authorship.

https://doi.org/10.1016/j.comppsych.2023.152442

Available online 5 December 2023

previous research has focused either on independent associations of total PA, MVPA, light-intensity PA and sedentary time, whereas only a few studies have taken into account the daily equilibrium between SB and PA in the association with biomarkers of health [9] or depression [10,11]. In order to take this equilibrium into account, Bakrania et al. [9] have suggested subtyping individuals according to both their SB and PA measured by accelerometers during a day. They considered individuals as 'highly sedentary' if they resided in quartiles 2 to 4 according to the sedentary time - light-intensity physical activity time ratio and as 'physical active' if they accumulated at least 150 min of MVPA per week. The cross-classification according to SB and MVPA status provided four PA behaviors labeled as: 1) "Couch potatoes" (low MVPA and high SB levels), 2) "Light movers" (low MVPA and low SB levels), 3) "Sedentary exercisers" (high MVPA and high SB levels) and 4) "Busy bees" (high MVPA and low SB levels). Applied in an English health survey, this classification revealed that Busy bees and Sedentary exercisers had lower body-mass index (BMI) and high levels of HDL-cholesterol compared to Couch potatoes. The Busy bees also had lower glycated hemoglobin [9]. Using the same classification, researchers in Lausanne attempted to replicate these findings. However, the Lausanne general population showed much lower levels of SB and higher levels of MVPA [12], which was in line with earlier surveys showing that within Europe the Swiss population had the second highest levels of exercising after the Swedish population [13]. After adaptation of the cutoffs for both SB and MVPA status, the Sedentary exercisers and Busy bees had a lower likelihood of smoking, obesity and diabetes than the Couch potatoes, which essentially was in line with the findings of the English study.

Regarding depression, although depressive disorders or symptoms have been shown to be associated with low PA and high SB [4,14–16], only very few studies have jointly assessed the effects of SB and MVPA. Among them, an internet-based study conducted in Japan found sufficient PA levels to be related with a lower risk of depressive symptoms, whereas SB levels were not associated with depressive symptoms [10]. However, there have been a large variety of measures used to assess PA and SB, and most studies relied on self-reported rather than objectively measured levels of PA and SB [16–18]. In the last two decades, actigraphy has been increasingly used. A recent systematic review and meta-analysis of 42 cross-sectional and prospective studies on the association between objectively measured PA and depression showed a statistically significant association between higher levels of PA and both a lower prevalence and incidence of depression [14]. This has recently been confirmed by a large-scale study of 95,529 individuals from the UK biobank [19]. This study also showed that the initial associations between PA and MDD were attenuated after controlling for substance use disorders (SUD), which are also associated with low PA [18]. One recent accelerometer-based study, that independently analyzed the effects of PA and SB found PA to moderate the association between SB and depressive symptoms [11]. However, many of these studies were hampered by the use of self-report depression questionnaires. Given that these instruments typically only take the few weeks prior to the assessment into account, potential long-term effects of past depressive episodes could not be assessed.

Moreover, very few studies have yet taken MDD subtypes into consideration, despite the fact that MDD is a heterogeneous disorder, by its symptom manifestations, aetiology, biological mechanisms, genetics and treatment response [20–23]. It has been hypothesized that depression subtypes are differently associated with biological mechanisms. Indeed the atypical subtype, mainly characterized by increased appetite and hypersomnia, has been shown to be more strongly related to metabolic dysregulation [24–31] and inflammation up-regulations [21–23] and the melancholic subtype to an overdrive of the hypothalamic-pituitary-adrenal (HPA) axis [32]. Among the rare studies that have addressed the associations between MDD subtypes and PA, Glaus et al. [24] observed a cross-sectional association between lifetime atypical MDD and self-reported lack of PA in the community, whereas a study including patients meeting criteria for MDD [33] found all remitted MDD subtypes (melancholic, atypical, combined and undifferentiated) to be associated with self-reported lower PA, whereas only current episodes of undifferentiated and melancholic subtypes were associated with lower PA. More recently, the Dutch NESDA study revealed associations of all of the three factor analytically derived depression symptom dimensions of mood/cognition, somatic/vegetative and sleep, with objectively measured lower levels of PA [34], whereas actigraphy-based data of our own study showed that the remitted atypical and melancholic subtypes as well as the current unspecified subtype were associated with lower levels of MVPA during a 14-day period [35]. The association of the remitted atypical and melancholic subtypes with lower levels of PA suggested that lower PA levels could be a trait marker in people with these MDD subtypes.

The aim of the present study was to test whether the four actigraphy-derived PA behaviors suggested by Bakrania et al. [9] are also associated with the four MDD subtypes: atypical, melancholic, combined and unspecified, in a large population-based cohort. Analyses were adjusted for conditions that are potentially associated with PA including socio-demographic factors, other CVRF, as well as anxiety disorders and SUD. In order to test whether the observed associations reflect traits or states, MDD was subdivided into current versus remitted disorders.

2. Methods

2.1. Sample selection

The present data stem from CoLaus|PsyCoLaus, a cohort study designed to investigate CVRF or cardiovascular diseases and mental disorders in the community. The methodological features of this study were previously described in detail [36,37]. Briefly, CoLaus|PsyColaus includes an original random sample of 6734 participants (age range: 35–75 years) selected from the residents of the city of Lausanne according to the civil register between 2003 and 2006 and followed up after 5 (Follow-up 1), 9 (Follow-up 2), and 13 years (Follow-up 3). The present analyses (Fig. 1) included participants who had worn a wrist accelerometer for a duration of 14 days at the 2nd physical follow-up (2014–2018) and had participated either at the 2nd or 3rd psychiatric follow-up. A total of 124 participants were excluded because of known bipolar or psychotic disorders as these disorders are likely to influence the PA level, resulting in a final sample of 2375 participants. Among them 148 met lifetime criteria for remitted MDD with atypical features, 254 for remitted MDD with melancholic features, 161 for remitted MDD with combined atypical-melancholic features, 441 for remitted MDD with unspecified features (with no atypical or melancholic features), 188 for current MDD and 1183 were exempt from lifetime MDD.

Among the participants of the physical exam with no exclusionary psychiatric disorders ($n = 4044$) those who could be included for the present analyses were younger (61.6 vs. 63.7 years, t-test = 1.2; $p < 0.01$), tended to have a higher education level (chi-square = 15.4; $p < 0.01$), were less likely to be diagnosed with diabetes (8.3% vs. 10.8%; chi-square = 7.5; $p < 0.01$) or hypertension (43.1% vs. 50.0%; chi-square = 19.1; $p < 0.0001$) as compared to those who could not be included. However, the two groups did not differ by sex, being of Caucasian origin, living or smoking status, alcohol consumption, BMI or the likelihood of being diagnosed with dyslipidemia.

The institutional Ethics Committee for clinical research of the Medical and Biological Faculty of the University of Lausanne, which afterwards became the Ethics Committee of the Canton of Vaud for human research, approved the CoLaus|PsyCoLaus study (www.cer-vd.ch; project number PB_2018–00038, reference 239/09) and all participants provided written informed consent. The study was performed in agreement with the Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation.

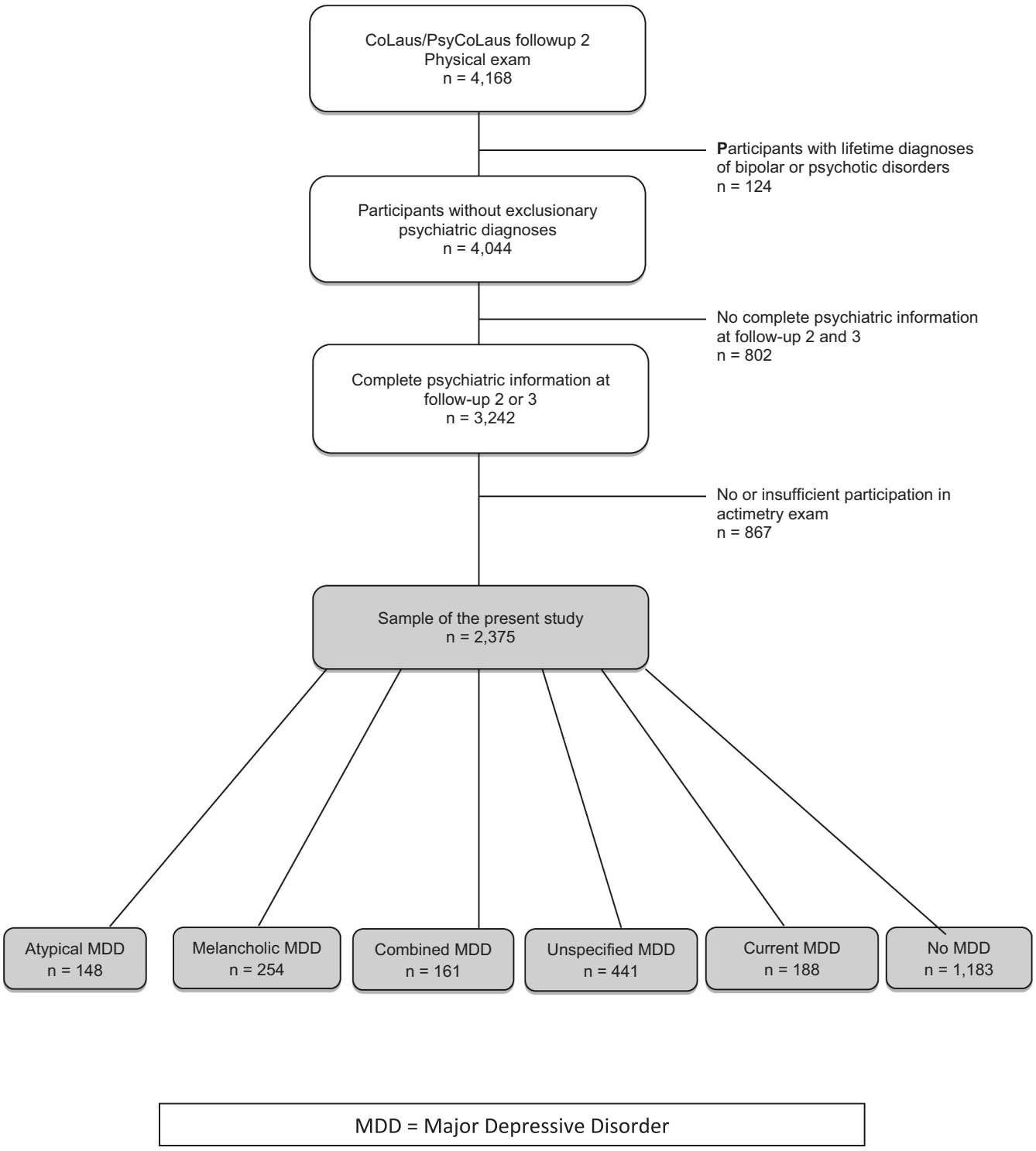


Fig. 1. Flow chart for the assessment of associations between physical activity and lifetime depression subtypes at the time of follow-up (2014–2018).

2.2. Measures

2.2.1. Physical activity behaviors

PA and SB were assessed according to the methodology described in Gubelmann et al. [12]. Briefly, participants were asked to wear a right-wrist-worn triaxial accelerometer (GENEActiv, Activinshights Ltd., United Kingdom) [38] continuously during 14 days in their usual living conditions. The devices were pre-programmed with a 50 Hz sampling frequency. Data were downloaded using the GENEActiv software version 2.9 (GENEactiv, Activinshights Ltd., United Kingdom) and collapsed into 60-s epoch files. To be considered valid, the diurnal wear-time had to be >10 h for a weekday and > 8 h for a weekend day. A minimum of 5 valid weekdays and 2 valid weekend days were required for this analysis. MVPA was derived using standard count-per-minute thresholds to classify the activity time. We used the R-package Actigraphy.R with the threshold of 100 [39,40], the GGIR version 1.5–9 (http://cran.r-project.org) [41,42]. The time each participant spent in low intensity PA (LIPA), MVPA and SB was averaged for all valid days. According to Bakrania et al. [9], activity behaviors were defined by the combination of PA and SB status with the adjusted cutoffs as suggested

by Gubelmann et al. [12]. Indeed, for PA status the cutoff proposed by Bakrania et al. [9] involving the dichotomization of the sample into those with and without 150 min of MVPA per week was not applicable in the Lausanne sample, because nearly all participants accumulated at least 150 min of MVPA per week. Hence applying more stringent criteria, high PA status was defined as being part of the second or third tercile according to the participant's average time with MVPA. The cutoff corresponded to 133 min of MVPA per day. According to this cutoff 67.3% were classified within high PA, whereas in the English study of Bakrania 55.2% of the sample fulfilled the much more lenient criterion for high PA. For SB status, Bakrania et al. defined high SB status as being part of the 2nd, 3rd or 4th quartile according to the ratio between the average SB time and the average LIPA time. Again, given that the participants of the Lausanne study spent much less time in the sedentary intensity band, the proposed dichotomization could not be used. Instead, high SB status was defined as being part of the 3rd tercile according to the ratio between the average SB time and the average LIPA time, corresponding to a cutoff of >7.2. This third of participants classified as sedentary also corresponded to the third of the Swiss population that described themselves as inactive [13]. As suggested by Bakrania et al. [9] PA status and SB status were then combined to form the four PA behaviors of 1) Couch potato (low PA and high SB), 2) Light mover (low PA and low SB), 3) Sedentary exerciser (high PA and high SB), and 4) Busy bee (high PA and low SB).

2.2.2. Mental disorders

Information on mental disorders including MDD, alcohol and drug use disorders was collected at baseline and follow-up using the French version [43] of the Diagnostic Interview for Genetic Studies (DIGS) [44], which has revealed excellent inter-rater reliability, and slightly lower reliability for the 6-week test-retest of mood and psychotic disorders [43] as well as SUD [45]. The DIGS was completed by the French version [46] of the anxiety section of the Schedule for Affective Disorders and Schizophrenia-Lifetime and Anxiety disorders (SADS-LA) [47], which revealed excellent inter-rater and fair-to-good test-retest reliability [46,48].The diagnoses for the present paper were based on the DSM-IV, which also includes specifiers for atypical or melancholic features during major depressive episodes (MDE). The specifier for atypical features requires mood reactivity and two of the following criteria: weight gain or increase in appetite, hypersomnia, leaden paralysis and longstanding pattern of interpersonal rejection sensitivity. The melancholic specifier requires a loss of pleasure or lack of reactivity and three of the following criteria: distinct quality of depressed mood, depression worse in the morning, early-morning awakening, psychomotor agitation or retardation, weight loss or guilt. We could not take into account the criterion 'distinct quality of depressed mood' because it was not assessed in the DIGS. According to these specifiers, each MDE was classified into 1) atypical, 2) melancholic, 3) combined atypical-melancholic (meeting criteria for both atypical and melancholic episodes) and 4) unspecified (not meeting criteria for atypical or melancholic episodes). Extending the approach suggested by Angst et al. [49], lifetime MDD was subtyped according to the occurrence of subtypes of episodes across lifespan into: 1) atypical MDD with at least one atypical (but no melancholic or combined) episode; 2) melancholic MDD with at least one melancholic (but no atypical or combined) episode; 3) combined MDD (one atypical-melancholic combined episode or at least one atypical and one melancholic episode); and 4) unspecified MDD (no atypical, melancholic or combined episode). In addition, these categories were subdivided into current MDD (presence of an MDE at the time of the actigraphy measure) or remitted MDD (MDD with offset prior to the actigraphy measure).

Interviews were conducted by master-level psychologists, who had been trained for a period of 1 to 2 months. All interviews were reviewed by an experienced senior psychologist. Socio-demographic characteristics were assessed with the DIGS at the second or third follow-up: sex, age, living along versus not as well as socio-economic status (SES) defined according to the Hollingshead scale [50]. In the case of missing socio-demographic data, the information from the questionnaire completed at the somatic assessment was taken as far as possible.

2.2.3. Somatic measures

The physical evaluation, which was conducted by trained nurses, included a standardized interview, a physical examination, as well as the completion of self-report questionnaires. During the interview, information on socio-demographic characteristics and smoking status (current or former smoking of at least 10 cigarettes per day) was collected. Body weight and height were objectively measured with participants being barefoot and in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a Seca® scale (Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca® (Hamburg, Germany) height gauge. Blood pressure was measured using an Omron® HEM-907 automated oscillometric sphygmomanometer after at least a 10-min rest in a seated position, and the average of the last two measurements was used. The diagnosis of hypertension was assigned according to the Joint National Committee (JNC) criteria, i.e., a systolic blood pressure of 140 mmHg or above, a diastolic blood pressure of 90 mmHg or above, or any antihypertensive treatment [51]. Venous blood samples were drawn after an overnight fast in order to measure the levels of glucose, HDL-cholesterol, LDL-cholesterol, triglycerides and insulin. The diagnosis of diabetes was assigned according to the Expert Committee on the Diagnosis and Classification of Diabetes criteria [52], i.e., a fasting glucose level of 7 mmol/l or above or antidiabetic treatment. The diagnosis of dyslipidemia was assigned according to the National Cholesterol Education Program (NCEP) Expert Panel (Adult Treatment Panel III, ATP III) criteria, i.e., fasting blood triglycerides of 2.2 mmol/l or above, LDL cholesterol of 4.1 mmol/l or above, HDL cholesterol of 1 mmol/l or less, or any hypolipidaemic treatment [53].

2.3. Statistical analysis

Socio-demographic data, the presence of other lifetime psychiatric disorders and the presence of CVRF (BMI, hypertension, diabetes, dyslipidemia and smoking status) at the follow-up were established for the four remitted MDD subtype groups, participants with current MDD and participants with no MDD. Differences were calculated across all the groups by sex- and age-adjusted logistic regression models for categorical outcomes or by multiple regression models for continuous outcomes. A total of 32 participants had remaining missing data for socio-demographic variables which were compensated with multiple imputations (Markov Chain Monte Carlo method and Rubin's multiple imputation strategy [54,55] using available data from the other socio-demographic variables. The four remitted MDD subtypes were retained, and current MDD was represented by all 4 current subtypes combined due to limited sample size in each category. The associations between PA behaviors, current MDD and remitted MDD subtypes were calculated using multinomial logistic regression models, where the outcome was composed of the four PA levels (taking the "Busy bee" category as the reference). In Model 1, the independent variables were the four remitted MDD subtypes and current MDD compared to no lifetime history of MDD, and adjustments were made for socio-demographic characteristics and a lifetime history of anxiety, alcohol and drug use disorders, either as comorbidities to MDD or else as primary disorders in participants with no MDD. Model 2 used the same adjustments as Model 1, but further adjusted for the presence of CVRF.

3. Results

Table 1 describes the socio-demographic characteristics of the whole sample and of the subgroups according to the presence of remitted MDD subtypes, current MDD and the absence of MDD. Overall, participants were 54.7% female, 28.6% living alone, and most had a slightly above-average SES level. Their mean age was 62.4 (s.d. 9.9) years. A total of 24.4% had lifetime anxiety disorders, 11.3% reached criteria for alcohol

Table 1
Socio-demographic and clinical characteristics of participants in the whole sample and according to remitted and current depression status.

Characteristic	Whole sample	MDD remitted subtypes§					No MDD[a]	
	$n = 2375$	Atypical $n = 148$	Melancholic $n = 254$	Combined $n = 161$	Unspecified $n = 441$	Current MDD $n = 188$	$n = 1183$	p *
Sex,								
Female, % (n)	54.7 (1300)	69.6 (103)	60.6 (154)	78.9 (127)	61.3 (267)	72.3 (136)	43.4 (513)	<0.0001
Age, years, mean (SD)	62.4 (9.9)	60.5 (8.8)	61.1 (9.6)	60.2 (8.8)	61.2 (9.5)	59.4 (8.6)	64.0 (10.3)	<0.0001
Living status								
Alone, % (n)	28.6 (649)	33.1 (49)	30.7 (78)	28.0 (45)	34.2 (151)	38.8 (73)	23.9 (283)	0.0003
SES mean (SD)	3.5 (1.2)	3.5 (1.2)	3.7 (1.1)	3.4 (1.2)	3.6 (1.2)	3.3 (1.3)	3.5 (1.2)	0.0934
Other lifetime psychiatric disorders, %								
Anxiety disorders[b] (n)	24.4 (579)	32.4 (48)	29.1 (74)	46.0 (74)	29.9 (132)	49.5 (93)	13.4 (158)	<0.0001
Alcohol ab/dep[c] (n)	11.3 (269)	10.8 (16)	14.2 (36)	8.1 (13)	12.7 (56)	11.7 (22)	10.7 (126)	0.0081
Drug[d] ab/dep[c] (n)	5.2 (123)	2.0 (3)	7.5 (19)	6.2 (10)	6.8 (30)	10.1 (19)	3.6 (42)	0.0115
Cardio-metabolic risk factors at follow-up								
BMI, mean (SD)	26.3 (4.7)	28.2 (5.4)	25.2 (4.3)	26.7 (4.8)	26.2 (4.6)	26.5 (5.2)	26.2 (4.6)	0.0008
Diabetes % (n)	8.3 (197)	8.1 (12)	3.9 (10)	8.1 (13)	9.3 (41)	5.3 (10)	9.4 (111)	0.8647
Hypertension % (n)	43.1 (1023)	37.8 (56)	37.8 (96)	36.7 (96)	40.4 (178)	38.8 (73)	47.4 (561)	0.9851
Dyslipidemia % (n)	39.0 (926)	35.1 (52)	35.4 (90)	34.8 (56)	41.0 (181)	36.7 (69)	40.4 (478)	0.6220
Current smoking % (n)	17.8 (423)	20.3 (30)	19.7 (50)	18.0 (29)	17.2 (76)	36.2 (68)	14.4 (170)	0.0004
Former smoking % (n)	39.8 (944)	37.2 (55)	43.7 (111)	39.1 (63)	43.3 (191)	30.3 (57)	39.5 (467)	0.3031

MDD, Major Depressive Disorder; § mutually exclusive categories; p = comparison across subtypes; * models adjusted for sex and age (sex and age adjusted for the alternate variable), BMI = Body Mass Index. SD, standard deviation, SES, Socio-economic status following Hollingshead's index: a value of 3 represents middle class.
[a] Excluding participants diagnosed with bipolar or psychotic disorders.
[b] Includes agoraphobia, generalized anxiety disorder, social phobia and panic disorder.
[c] Abuse or dependence.
[d] Includes marijuana, cocaine, stimulants, sedatives, narcotics, hallucinogens, solvents.

abuse/dependence, and 5.2% had drug abuse/dependence. The mean BMI of the sample was 26.3 (s.d.: 4.7), 8.3% had diabetes, 43.1% hypertension, 39.0% dyslipidemia while 17.8% and 39.8% were current and former smokers, respectively. There were significant differences across the MDD subgroups for all the given socio-demographic characteristics, except for SES. Clinical characteristics were found to differ across all subgroups for anxiety and alcohol use disorders, BMI and current smoking.

Within the whole sample 521 (21.9%) were Couch potatoes, 268 (11.3%) were Light movers, 279 (11.8%) were Sedentary exercisers and 1307 (55.0%) were Busy bees (Table 2). The two models provide the results of the adjusted multinominal logistic regression analysis of the associations between the MDD diagnostic grouping as the independent variable and the four-level PA as the dependent variable. Model 1 is adjusted for sociodemographic variables and other psychiatric disorders, Model 2 also for CVRF. Regardless of these adjustments, the two models revealed that the remitted combined subtype was associated with a higher likelihood of being a Light mover rather than a Busy bee, compared to participants with no MDD.

4. Discussion

The main finding of this first community study assessing the associations between MDD subtypes and objectively measured PA behaviors was that people with the remitted combined atypical-melancholic MDD subtype had a higher likelihood of being part of the category of Light movers than that of Busy bees as compared to those with no depression. Considering that the Light mover and the Busy bee patterns differ in MVPA, but not SB status, our results suggest that people with the remitted combined atypical-melancholic MDD subtype essentially differed from those with no MDD with respect to lower levels of MVPA, but not with respect to SB status after controlling for socio-demographic characteristics, a history of anxiety, alcohol and drug use disorders as well as CVRF. Our observation that only MVPA levels but not SB levels are associated with a MDD subtype is in line with the study of Liao [10]. Similarly, in a prospective accelerometer-based study focusing on SB to predict incident depressive symptoms, high SB was not associated with incident depressive symptoms, whereas lower levels of daily LIPA were associated with an increased risk of symptoms, but only in women [56]. Moreover, our observation that the light mover and busy bee patterns, which do not differ by SB but by PA status, entailed differential risk of combined MDD is consistent with the results of a recent accelerometer-based study that documented PA to moderate the association between SB and depressive symptoms [11].

Combined atypical-melancholic MDD, which has been found to be associated with less active PA behavior in our study is likely to be the most severe subtype given that it requires two episodes or a complex episode with the presence of both atypical and melancholic symptoms. This may be one of the reasons why only people with this but not with other MDD subtypes differed from those with no MDD in PA behaviors. This finding is consistent with our recent actigraphy-based finding of an association of both the atypical and melancholic subtypes with lower MVPA levels [35], although the previous paper used MVPA as a continuous variable and did not simultaneously take SB status into account. Our new finding is somehow different from the analysis of the baseline data of the same study supporting an association of lifetime atypical rather than combined MDD with self-reported physical inactivity [24]. This latter discrepant result may be due to the self-reported measure of physical inactivity ([24] rather than an objectively measured one. Comparisons with the results of the NESDA study are difficult given the use of a depression dimension in NESDA rather than depression subtypes [34,57]. However, the results of these studies concur in the observation of associations between PA and episodes with atypical and partially melancholic depression symptoms. The atypical subtype has been shown to be linked with inflammatory [23,58] and metabolic factors [21,28,59], which in turn are modulated by PA [60,61]. The observed association between the remitted combined MDD subtype and PA behaviors in the present study indicates that lower PA is not restricted to the duration of depressive episodes and could be either the consequence of depressive episodes with melancholic and atypical features or a vulnerability factor for atypical and melancholic episodes. However, the cross-sectional nature of the present data impedes us to draw conclusions regarding the direction of this association. A prospective study documented an association between self-reported PA and a reduced risk of incident MDD during a two-year period [62]. Moreover, a two-sample Mendelian Randomization analysis conducted in a large database also confirmed a protective relationship between accelerometer-based activity and MDD [63] although there was no

Table 2
Associations among physical activity behaviors and remitted and current MDD subtypes, with serial adjustments for potential confounders.

	Activity behaviors (dependent variables) §									
	Couch potato			Light mover			Sedentary exerciser			Busy bee°
	$n = 521$			$n = 268$			$n = 279$			$n = 1307$
	Crude % / mean	Model 1 OR[1] (95% CI)	Model 2 OR[2] (95% CI)	Crude % / mean	Model 1 OR[1] (95% CI)	Model 2 OR[2] (95% CI)	Crude % / mean	Model 1 OR[1] (95% CI)	Model 2 OR[2] (95% CI)	Crude % / mean
Variables of interest										
MDD subtypes §										
Remitted Atypical %	5.2	1.0 (0.6–1.6)	0.8 (0.5–1.3)	6.3	1.2 (0.7–2.1)	1.0 (0.5–1.7)	5.7	0.8 (0.5–1.5)	0.8 (0.5–1.5)	6.7
Remitted Melancholic %	9.8	1.0 (0.7–1.5)	1.1 (0.7–1.6)	10.1	1.1 (0.7–1.8)	1.1 (0.7–1.9)	13.3	1.1 (0.7–1.7)	1.2 (0.8–1.8)	10.6
Remitted Combined %	4.8	1.1 (0.7–1.8)	0.9 (0.6–1.6)	10.1	**2.0** (1.2–3.3)**	**1.8* (1.1–3.1)**	5.7	0.9 (0.5–1.5)	0.8 (0.5–1.5)	7.1
Remitted Unspecified %	16.3	0.9 (0.7–1.2)	0.9 (0.6–1.2)	16.0	0.9 (0.6–1.3)	0.9 (0.6–1.3)	18.3	0.8 (0.6–1.2)	0.8 (0.6–1.2)	20.1
Current MDD[a] %	7.7	1.5 (1.0–2.3)	1.2 (0.8–1.9)	6.7	1.2 (0.7–2.0)	1.0 (0.5–1.7)	7.5	0.9 (0.5–1.6)	1.0 (0.6–1.6)	8.3
No MDD %	56.2	ref	ref	50.8	ref	ref	49.5	ref	ref	47.1
Adjustments										
Socio-demographics										
Female %	38.0	**0.3*** (0.3–0.4)**	**0.4*** (0.3–0.5)**	61.6	0.8 (0.6–1.1)	1.0 (0.7–1.3)	44.1	**0.5*** (0.4–0.7)**	**0.5*** (0.4–0.7)**	62.3
Age, years mean (SD)	65.8 (10.5)	**1.1*** (1.0–1.1)**	**1.1*** (1.0–1.1)**	67.3 (10.3)	**1.1*** (1.1–1.1)**	**1.1*** (1.1–1.1)**	58.5 (8.9)	**1.0** (1.0–1.0)**	**1.1** (1.0–1.0)**	60.7 (8.9)
Living alone %	29.8	1.2 (1.0–1.6)	1.2 (0.9–1.5)	37.7	1.3 (1.0–1.8)	1.2 (0.9–1.7)	29.8	**1.6** (1.2–2.2)**	**1.6** (1.2–2.2)**	26.0
SES mean (SD)	3.7 (1.1)	**1.3*** (1.2–1.5)**	**1.4*** (1.3–1.6)**	3.4 (1.2)	1.1 (1.0–1.2)	**1.2* (1.0–1.3)**	3.9 (1.1)	**1.4*** (1.3–1.6)**	**1.4*** (1.3–1.6)**	3.3 (1.2)
Other lifetime psychiatric disorders										
Anxiety disorders[b] %	20.7	1.0 (0.7–1.3)	1.0 (0.8–1.4)	20.9	0.9 (0.6–1.2)	0.9 (0.6–1.2)	27.2	1.2 (0.9–1.6)	1.1 (0.8–1.6)	25.9
Alcohol ab/dep[c] %	13.8	1.2 (0.9–1.7)	1.1 (0.8–1.6)	9.7	1.1 (0.7–1.7)	0.9 (0.6–1.5)	12.2	0.9 (0.6–1.5)	0.9 (0.6–1.5)	10.5
Drug[d] ab/dep[c] %	3.1	**0.5* (0.3–0.9)**	**0.5* (0.3–0.9)**	3.7	1.0 (0.5–2.0)	0.9 (0.5–2.0)	6.8	0.8 (0.5–1.4)	0.9 (0.5–1.5)	6.0
Cardio-metabolic risk factors										
BMI, mean (SD)	27.6 (5.0)	–	**1.1*** (1.1–1.1)**	27.4 (5.0)	–	**1.1*** (1.0–1.1)**	25.8 (4.3)	–	1.0 (1.0–1.0)	25.6 (4.4)
Diabetes %	15.6	–	**1.5* (1.1–2.3)**	13.4	–	1.3 (0.8–2.1)	3.2	–	0.6 (0.3–1.2)	5.4
Hypertension %	56.2	–	1.2 (0.9–1.5)	60.1	–	**1.5* (1.1–2.0)**	35.1	–	1.02 (0.8–1.4)	36.0
Dyslipidemia %	47.4	–	1.1 (0.9–1.4)	49.6	–	1.3 (0.9–1.7)	38.4	–	1.3 (1.0–1.7)	33.6
Current smoking %	21.5	–	**1.7*** (1.3–2.4)**	21.3	–	**2.0*** (1.4–3.0)**	12.2	–	0.7 (0.4–1.0)	16.8
Former smoking %	38.4	–	0.9 (0.7–1.1)	41.4	–	1.1 (0.8–1.5)	41.9	–	1.1 (0.8–1.4)	39.5

***$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.** Statistically significant values are in bold.
§ mutually exclusive categories; ° reference category; MDD = major depressive disorder; SES = socio-economic status; BMI = Body Mass Index.
[1] Model computed according to multinomial logistic regression (reference category = Busy bee), adjusted for sex, age, living status, and SES and other lifetime psychiatric disorders.
[2] Model computed according to multinomial logistic regression (reference category = Busy bee), adjusted for sex, age, living status, SES, other lifetime psychiatric disorders and cardio-metabolic risk factors.
[a] All current MDD subtypes grouped together.
[b] Includes agoraphobia, generalized anxiety disorder, social phobia and panic disorder.
[c] Abuse or dependence.
[d] Includes marijuana, cocaine, stimulants, sedatives, narcotics, hallucinogens, solvents.

statistically significant relationship between MDD and accelerometer-based activity [63], suggesting that low PA is a risk factor for rather than a consequence of MDD. However, as these studies only assessed the overall MDD category and not subtypes, it remains elusive to which degree the specific MDD subtypes could contribute to the observed associations. Hence, prospective or Mendelian Randomization studies including the assessment of MDD subtypes and objective PA measures are crucial to establish the direction of the association between specific subtypes and PA. Moreover, as suggested by a recent prospective study the association between PA levels and MDD my vary by sex [56], future studies should also test interactions by sex and conduct stratified analyses if indicated. Moreover, according to a recent review not only the overall daily PA pattern, but also the timing of PA may be associated with an increase of subsequent depressive symptoms [15]. Hence, it would be interesting to test whether lower PA during the morning or higher PA late in the evening are associated with the risk of depression.

Concerning the biological mechanisms underlying the association between PA and MDD, research has shown that PA may induce the following changes: a decrease in hippocampal activation and an increase in cortical inhibition [64], an increase in neurogenesis [60,64], a

diminution of oxidative markers [60], improvement in monoaminergic neurotransmission [61], changes in the Hypothalamic-Pituitary-Adrenal (HPA) Axis [61] and reduction of inflammation (for e.g. reduction in pro-inflammatory cytokines and changes in the kynurenine pathway as a result of an increase of PGC1-α gene expression) [60,61]. These potential changes are contrary to key mechanisms postulated to be enhanced in the pathogenesis of depression [60,61,64]. It may therefore be that the effects of PA help counteract the neurobiological mechanisms underlying the development of MDD.

The absence of an association between current MDD subtypes and PA in the present study is surprising and contrasts with results of some other previous research [17,57,65]. Indeed, a meta-analysis has revealed that currently depressed persons are more likely to have lower levels of self-reported PA compared to a healthy person [17]. Moreover, the NESDA study showed that individuals with current depressive or anxiety disorders [57] had lower objectively measured PA than normal controls. Given that the association with PA behaviors differed across MDD subtypes in remitted people in our study, the lack of subtyping current MDD due to the small sample size may be a reason for our negative finding in people with current MDD.

The findings of the present study should be interpreted in the context of several limitations. First, the observational nature of our study impedes the establishment of causality. Second, as mentioned, because the number of participants with a current episode of MDD was low, we could not determine the differential associations between current MDD subtypes analyzed separately and PA behaviors. Third, given the time gap of one year between the physical exam including actigraphy and the psychiatric evaluation, the presence of the current MDD vs. remitted episode distinction with respect to the moment of the actigraphy needed to be based on the participant's reporting of the dates of onset and offset of depressive episodes, which may have led to misclassification of current and remitted episodes and an underestimation of the established associations. Fourth, wearing the accelerometer can influence normal PA behavior, by encouraging participants to exercise more than usual, and might therefore not represent a participant's usual PA level. Fifth, the sample was derived from an urban area of Switzerland with a mean age of >60 years, which limits the generalizability of our findings.

The results of the present study have several scientific and clinical implications. The differential associations of MDD subtypes with PA behaviors further emphasize the importance of subtyping MDD when studying its associations with CVRF. They also suggest that patients with atypical and melancholic episodes in particular tend to have long-standing reduced PA behaviors, which may predispose them to an increased risk of cardiovascular diseases. However, although the atypical subtype has already been shown to be prospectively associated with a steeper increase in BMI and glucose as well as with an increased risk of the metabolic syndrome [59], the long-term association of this subtype with cardiovascular diseases and the specific role of lower PA in this potential association still needs to be demonstrated. As the lack of PA is a well-established CVRF [7], encouraging people to increase their PA may be particularly important in those with atypical and melancholic episodes in order to decrease their cardiovascular risk. Finally, higher engagement in PA might also help prevent further episodes of MDD, which should still be shown in future prospective studies using MDD subtypes and objective measures of PA.

In conclusion, by demonstrating associations between the remitted combined MDD subtype and lower levels of PA, our findings suggest that lower PA is not restricted to the duration of depressive episodes in people with atypical and melancholic episodes. The lack of PA in this group of depressive patients exposes them to an additional long-term cardiovascular risk and measures to increase PA may be particularly fruitful in this MDD subgroup.

Funding

The CoLaus|PsyCoLaus study was supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401, 33CS30_177535 and 3247730_204523) and the Swiss Personalized Health Network (grant 2018DRI01).

CRediT authorship contribution statement

Maulde Rovero: Conceptualization, Methodology, Resources, Writing – original draft. **Martin Preisig:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Pedro Marques-Vidal:** Conceptualization, Data curation, Methodology, Resources, Visualization, Writing – review & editing. **Marie-Pierre F. Strippoli:** Data curation, Methodology, Resources, Validation, Writing – review & editing. **Peter Vollenweider:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Julien Vaucher:** Funding acquisition, Methodology, Project administration, Resources, Writing – review & editing. **Alexandre Berney:** Writing – review & editing. **Kathleen R. Merikangas:** Writing – review & editing. **Caroline L. Vandeleur:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Jennifer Glaus:** Conceptualization, Investigation, Methodology, Resources, Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

None.

Data availability

The data of CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch. Proposals requiring baseline data only, will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

Acknowledgments

We express our gratitude to the Lausanne inhabitants who volunteered to participate in the CoLaus|PsyCoLaus study. We would also like to thank all the staff involved in the study. The authors would also like to thank all the investigators of the CoLaus|PsyCoLaus study, in particular Prof. G. Waeber.

References

[1] Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 2011; 9:90. https://doi.org/10.1186/1741-7015-9-90.

[2] Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–105. https://doi.org/10.1001/jama.289.23.3095.

[3] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72:334–41. https://doi.org/10.1001/jamapsychiatry.2014.2502.

[4] Huang Y, Li L, Gan Y, Wang C, Jiang H, Cao S, et al. Sedentary behaviors and risk of depression: a meta-analysis of prospective studies. Transl Psychiatry 2020;10:26. https://doi.org/10.1038/s41398-020-0715-z.

[5] Jingjie W, Yang L, Jing Y, Ran L, Yiqing X, Zhou N. Sedentary time and its association with risk of cardiovascular diseases in adults: an updated systematic review and meta-analysis of observational studies. BMC Public Health 2022;22: 286. https://doi.org/10.1186/s12889-022-12728-6.

[6] Pandey A, Salahuddin U, Garg S, Ayers C, Kulinski J, Anand V, et al. Continuous dose-response association between sedentary time and risk for cardiovascular disease: a Meta-analysis. JAMA Cardiol 2016;1:575–83. https://doi.org/10.1001/jamacardio.2016.1567.

[7] Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Lancet physical activity series working G, effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380:219–29. https://doi.org/10.1016/S0140-6736(12)61031-9.

[8] Posadzki P, Pieper D, Bajpai R, Makaruk H, Konsgen N, Neuhaus AL, et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. BMC Public Health 2020;20:1724. https://doi.org/10.1186/s12889-020-09855-3.

[9] Bakrania K, Edwardson CL, Bodicoat DH, Esliger DW, Gill JM, Kazi A, et al. Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. BMC Public Health 2016;16:25. https://doi.org/10.1186/s12889-016-2694-9.

[10] Liao Y, Shibata A, Ishii K, Oka K. Independent and combined associations of physical activity and sedentary behavior with depressive symptoms among Japanese adults. Int J Behav Med 2016;23:402–9. https://doi.org/10.1007/s12529-015-9484-0.

[11] Werneck AO, Kandola A, Tebar WR, Silva DR, Stubbs B, Christofaro DGD. Does physical activity moderate the association between device-measured sedentary time patterns and depressive symptoms in adults? Braz J Psychiatry 2022;44: 584–9. https://doi.org/10.47626/1516-4446-2022-2533.

[12] Gubelmann C, Vollenweider P, Marques-Vidal P. Of weekend warriors and couch potatoes: socio-economic determinants of physical activity in Swiss middle-aged adults. Prev Med 2017;105:350–5. https://doi.org/10.1016/j.ypmed.2017.10.016.

[13] Lamprecht M, Fischer A, Stamm HP. Sport Suisse 2014: Activité et consommation sportives de la population suisse. Macolin: Office fédéral du sport OFSPO; 2014. https://www.sportobs.ch/inhalte/Downloads/Sport_Schweiz_2014_f.pdf.

[14] Gianfredi V, Blandi L, Cacitti S, Minelli M, Signorelli C, Amerio A, et al. Depression and objectively measured physical activity: a systematic review and meta-analysis. Int J Environ Res Public Health 2020:17. https://doi.org/10.3390/ijerph17103738.

[15] Gianfredi V, Ferrara P, Pennisi F, Casu G, Amerio A, Odone A, et al. Association between daily pattern of physical activity and depression: a systematic review. Int J Environ Res Public Health 2022:19. https://doi.org/10.3390/ijerph19116505.

[16] Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, et al. Association between physical activity and risk of depression: a systematic review and meta-analysis. JAMA Psychiatry 2022;79:550–9. https://doi.org/10.1001/jamapsychiatry.2022.0609.

[17] Schuch F, Vancampfort D, Firth J, Rosenbaum S, Ward P, Reichert T, et al. Physical activity and sedentary behavior in people with major depressive disorder: a systematic review and meta-analysis. J Affect Disord 2017;210:139–50. https://doi.org/10.1016/j.jad.2016.10.050.

[18] Suetani S, Stubbs B, McGrath JJ, Scott JG. Physical activity of people with mental disorders compared to the general population: a systematic review of longitudinal cohort studies. Soc Psychiatry Psychiatr Epidemiol 2019;54:1443–57. https://doi.org/10.1007/s00127-019-01760-4.

[19] Dennison CA, Legge SE, Bracher-Smith M, Menzies G, Escott-Price V, Smith DJ, et al. Association of genetic liability for psychiatric disorders with accelerometer-assessed physical activity in the UK biobank. PLoS One 2021;16:e0249189. https://doi.org/10.1371/journal.pone.0249189.

[20] Harald B, Gordon P. Meta-review of depressive subtyping models. J Affect Disord 2012;139:126–40. https://doi.org/10.1016/j.jad.2011.07.015.

[21] Milaneschi Y, Lamers F, Berk M, Penninx B. Depression heterogeneity and its biological underpinnings: toward Immunometabolic depression. Biol Psychiatry 2020;88:369–80. https://doi.org/10.1016/j.biopsych.2020.01.014.

[22] Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med 2013;11:129. https://doi.org/10.1186/1741-7015-11-129.

[23] Woelfer M, Kasties V, Kahlfuss S, Walter M. The role of depressive subtypes within the neuroinflammation hypothesis of major depressive disorder. Neuroscience 2019;403:93–110. https://doi.org/10.1016/j.neuroscience.2018.03.034.

[24] Glaus J, Vandeleur C, Gholam-Rezaee M, Castelao E, Perrin M, Rothen S, et al. Atypical depression and alcohol misuse are related to the cardiovascular risk in the general population. Acta Psychiatr Scand 2013;128:282–93. https://doi.org/10.1111/acps.12057.

[25] Hasler G, Pine DS, Gamma A, Milos G, Ajdacic V, Eich D, et al. The associations between psychopathology and being overweight: a 20-year prospective study. Psychol Med 2004;34:1047–57. https://doi.org/10.1017/s0033291703001697.

[26] Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 2013;18: 692–9. https://doi.org/10.1038/mp.2012.144.

[27] Lamers F, Beekman AT, van Hemert AM, Schoevers RA, Penninx BW. Six-year longitudinal course and outcomes of subtypes of depression. Br J Psychiatry 2016; 208:62–8. https://doi.org/10.1192/bjp.bp.114.153098.

[28] Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, et al. Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. JAMA Psychiatry 2014;71:880–8. https://doi.org/10.1001/jamapsychiatry.2014.411.

[29] Ottino C, Strippoli MF, Gholam M, Lasserre AM, Vandeleur CL, Vollenweider P, et al. Short-term and long-term effects of major depressive disorder subtypes on obesity markers and impact of sex on these associations. J Affect Disord 2022;297: 570–8. https://doi.org/10.1016/j.jad.2021.10.057.

[30] Silva DA, Coutinho E, Ferriani LO, Viana MC. Depression subtypes and obesity in adults: a systematic review and meta-analysis. Obes Rev 2020;21:e12966. https://doi.org/10.1111/obr.12966.

[31] Onofre Ferriani L, Alves Silva D, Viana MC. Atypical depression is associated with metabolic syndrome: a systematic review. Actas Esp Psiquiatr 2022;50:266–75.

[32] Antonijevic IA. Depressive disorders - is it time to endorse different pathophysiologies? Psychoneuroendocrinology 2006;31:1–15. https://doi.org/10.1016/j.psyneuen.2005.04.004.

[33] Rahe C, Khil L, Wellmann J, Baune BT, Arolt V, Berger K. Impact of major depressive disorder, distinct subtypes, and symptom severity on lifestyle in the BiDirect study. Psychiatry Res 2016;245:164–71. https://doi.org/10.1016/j.psychres.2016.08.035.

[34] Difrancesco S, Penninx B, Riese H, Giltay EJ, Lamers F. The role of depressive symptoms and symptom dimensions in actigraphy-assessed sleep, circadian rhythm, and physical activity. Psychol Med 2022;52:2760–6. https://doi.org/10.1017/S0033291720004870.

[35] Glaus J, Kang SJ, Guo W, Lamers F, Strippoli MF, Leroux A, et al. Objectively assessed sleep and physical activity in depression subtypes and its mediating role in their association with cardiovascular risk factors. J Psychiatr Res 2023;163: 325–36. https://doi.org/10.1016/j.jpsychires.2023.05.042.

[36] Firmann M, Mayor V, Vidal PM, Bochud M, Pecoud A, Hayoz D, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovasc Disord 2008;8:6. https://doi.org/10.1186/1471-2261-8-6.

[37] Preisig M, Waeber G, Vollenweider P, Bovet P, Rothen S, Vandeleur C, et al. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC Psychiatry 2009;9:9. https://doi.org/10.1186/1471-244X-9-9.

[38] Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, Eston RG. Validation of the GENEA accelerometer. Med Sci Sports Exerc 2011;43:1085–93. https://doi.org/10.1249/MSS.0b013e31820513be.

[39] Di J, Spira A, Bai J, Urbanek J, Leroux A, Wu M, et al. Joint and individual representation of domains of physical activity, sleep, and circadian rhythmicity. Stat Biosci 2019;11:371–402. https://doi.org/10.1007/s12561-019-09236-4.

[40] Buman MP, Winkler EA, Kurka JM, Hekler EB, Baldwin CM, Owen N, et al. Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005-2006. Am J Epidemiol 2014;179:323–34. https://doi.org/10.1093/aje/kwt292.

[41] van Hees VT, Sabia S, Anderson KN, Denton SJ, Oliver J, Catt M, et al. A novel, open access method to assess sleep duration using a wrist-worn accelerometer. PLoS One 2015;10:e0142533. https://doi.org/10.1371/journal.pone.0142533.

[42] Migueles JH, Cadenas-Sanchez C, Rowlands AV, Henriksson P, Shiroma EJ, Acosta FM, et al. Comparability of accelerometer signal aggregation metrics across placements and dominant wrist cut points for the assessment of physical activity in adults. Sci Rep 2019;9:18235. https://doi.org/10.1038/s41598-019-54267-y.

[43] Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. Eur Arch Psychiatry Clin Neurosci 1999;249:174–9. https://doi.org/10.1007/s004060050084.

[44] Nurnberger JI, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH genetics initiative. Arch Gen Psychiatry 1994;51: 849–59. discussion 863-844, https://doi.org/10.1001/archpsyc.1994.03950110009002.

[45] Berney A, Preisig M, Matthey ML, Ferrero F, Fenton BT. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of alcohol and drug diagnoses. Drug Alcohol Depend 2002;65:149–58. https://doi.org/10.1016/s0376-8716(01)00156-9.

[46] Leboyer M, Maier W, Teherani M, Lichtermann D, D'Amato T, Franke P, et al. The reliability of the SADS-LA in a family study setting. Eur Arch Psychiatry Clin Neurosci 1991;241:165–9. https://doi.org/10.1007/BF02219716.

[47] Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837–44. https://doi.org/10.1001/archpsyc.1978.01770310043002.

[48] Rougemont-Buecking A, Rothen S, Jeanpretre N, Lustenberger Y, Vandeleur CL, Ferrero F, et al. Inter-informant agreement on diagnoses and prevalence estimates of anxiety disorders: direct interview versus family history method. Psychiatry Res 2008;157:211–23. https://doi.org/10.1016/j.psychres.2006.04.022.

[49] Angst J, Gamma A, Benazzi F, Ajdacic V, Rossler W. Melancholia and atypical depression in the Zurich study: epidemiology, clinical characteristics, course, comorbidity and personality. Acta Psychiatr Scand Suppl 2007:72–84. https://doi.org/10.1111/j.1600-0447.2007.00965.x.

[50] Hollingshead AB. Four factor index of social status. New Haven, CT: Yale University Press; 1975.
[51] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. Detection, evaluation, and treatment of high blood pressure. Hypertension 2003; 42:1206–52. https://doi.org/10.1161/01.HYP.0000107251.49515.c2.
[52] Expert Committee on the D, Classification of Diabetes M. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26(Suppl. 1):S5–20. https://doi.org/10.2337/diacare.26.2007.s5.
[53] Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97. https://doi.org/10.1001/jama.285.19.2486.
[54] Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ - Brit Med J 2009:339. https://doi.org/10.1136/bmj.b2393.
[55] Rubin DB. Multiple imputation for nonresponse in surveys. New Jersey, USA: Hoboken; 2004.
[56] Konopka MJ, Kohler S, Stehouwer CDA, Schaper NC, Henry RMA, van der Kallen CJH, et al. Accelerometer-derived sedentary time and physical activity and the incidence of depressive symptoms - the Maastricht study. Psychol Med 2020; 52:1–8. https://doi.org/10.1017/S0033291720004924.
[57] Difrancesco S, Lamers F, Riese H, Merikangas KR, Beekman ATF, van Hemert AM, et al. Sleep, circadian rhythm, and physical activity patterns in depressive and anxiety disorders: a 2-week ambulatory assessment study. Depress Anxiety 2019; 36:975–86. https://doi.org/10.1002/da.22949.
[58] Glaus J, von Kanel R, Lasserre AM, Strippoli MF, Vandeleur CL, Castelao E, et al. Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. Psychol Med 2018;48:961–73. https://doi.org/10.1017/S0033291717002744.
[59] Lasserre AM, Strippoli MF, Glaus J, Gholam-Rezaee M, Vandeleur CL, Castelao E, et al. Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population. Mol Psychiatry 2017;22:1026–34. https://doi.org/10.1038/mp.2016.178.
[60] Schuch FB, Deslandes AC, Stubbs B, Gosmann NP, Silva CT, Fleck MP. Neurobiological effects of exercise on major depressive disorder: a systematic review. Neurosci Biobehav Rev 2016;61:1–11. https://doi.org/10.1016/j.neubiorev.2015.11.012.
[61] Ignacio ZM, da Silva RS, Plissari ME, Quevedo J, Reus GZ. Physical exercise and Neuroinflammation in major depressive disorder. Mol Neurobiol 2019;56: 8323–35. https://doi.org/10.1007/s12035-019-01670-1.
[62] Choi KW, Zheutlin AB, Karlson RA, Wang MJ, Dunn EC, Stein MB, et al. Physical activity offsets genetic risk for incident depression assessed via electronic health records in a biobank cohort study. Depress Anxiety 2020;37:106–14. https://doi.org/10.1002/da.22967.
[63] Choi KW, Chen CY, Stein MB, Klimentidis YC, Wang MJ, Koenen KC, et al. Assessment of bidirectional relationships between physical activity and depression among adults: a 2-sample Mendelian randomization study. JAMA Psychiatry 2019; 76:399–408. https://doi.org/10.1001/jamapsychiatry.2018.4175.
[64] Gourgouvelis J, Yielder P, Murphy B. Exercise promotes neuroplasticity in both healthy and depressed brains: an fMRI pilot study. Neural Plast 2017;2017: 8305287. https://doi.org/10.1155/2017/8305287.
[65] Minaeva O, Booij SH, Lamers F, Antypa N, Schoevers RA, Wichers M, et al. Level and timing of physical activity during normal daily life in depressed and non-depressed individuals. Transl Psychiatry 2020;10:259. https://doi.org/10.1038/s41398-020-00952-w.