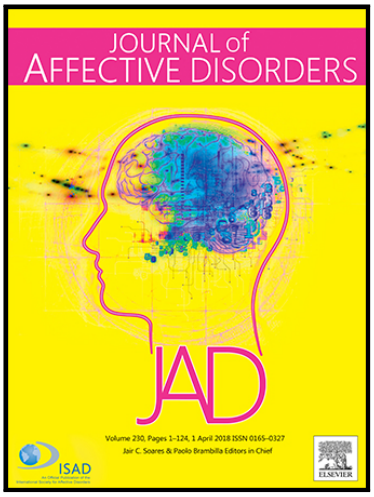

Prospective associations between multiple lifestyle behaviors and depressive symptoms

André O. Werneck , Davy Vancampfort , Brendon Stubbs , Danilo R. Silva , Gabriel G. Cucato , Diego G.D. Christofaro , Raul D. Santos , Raphael M. Ritti-Dias , Márcio S. Bittencourt

PII: S0165-0327(21)01449-X
DOI: https://doi.org/10.1016/j.jad.2021.12.131
Reference: JAD 14237

To appear in: *Journal of Affective Disorders*

Received date: 18 August 2021
Revised date: 13 December 2021
Accepted date: 31 December 2021

Please cite this article as: André O. Werneck , Davy Vancampfort , Brendon Stubbs , Danilo R. Silva , Gabriel G. Cucato , Diego G.D. Christofaro , Raul D. Santos , Raphael M. Ritti-Dias , Márcio S. Bittencourt , Prospective associations between multiple lifestyle behaviors and depressive symptoms, *Journal of Affective Disorders* (2022), doi: https://doi.org/10.1016/j.jad.2021.12.131

Prospective associations between multiple lifestyle behaviors and depressive symptoms

Association between lifestyle behaviors and depressive symptoms

André O. Werneck[1,*] andreowerneck@gmail.com, Davy Vancampfort[2], Brendon Stubbs[3], Danilo R. Silva[4], Gabriel G. Cucato[5], Diego G. D. Christofaro[6], Raul D. Santos[7,8], Raphael M. Ritti-Dias[9], Márcio S. Bittencourt[7,10,11]

[1]Center for Epidemiological Research in Nutrition and Health, Department of Nutrition, School of Public Health, University of São Paulo (USP), São Paulo, Brazil
[2]Department of Rehabilitation Sciences, KU Leuven, University of Leuven, Leuven, Belgium
[3]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, Box SE5 8AF, United Kingdom and South London and Maudsley NHS Foundation Trust, London, UK
[4]Department of Physical Education, Federal University of Sergipe - UFS, São Cristóvão, Brazil
[5]Department of Sport, Exercise & Rehabilitation, Northumbria University, Newcastle Upon Tyne, UK
[6]Department of physical education, Universidade Estadual Paulista "Júlio de Mesquita Filho", Presidente Prudente, Brazil
[7]Hospital Israelita Albert Einstein, São Paulo, Brazil
[8]Heart Institute (InCor), University of São Paulo Medical School Hospital, Sao Paulo, Brazil
[9]Post-graduate Program in Rehabilitation Sciences, Universidade Nove de Julho, São Paulo, Brazil
[10]Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, Brazil
[11]Center for Clinical and Epidemiological Research, University Hospital, University of São Paulo, Brazil

[*]**Corresponding author:** André O. Werneck, MSc, Center for Epidemiological Research in Nutrition and Health, Department of Nutrition, School of Public Health, Universidade de São Paulo (USP), Av. Dr. Arnaldo 715 Cerqueira César, 01246-904, São Paulo, Brazil

Highlights

- The maintenance of physical inactivity and risky drinking was associated with incident elevated depressive symptoms (DS)
- The incidence of physical inactivity and risky drinking was associated with incident elevated DS
- Maintenance and incident elevated DS were associated with physical inactivity and risky alcohol drinking

Abstract

Background: Our aim was to analyze the associations between multiple lifestyle behaviors and depressive symptoms.
Methods: We included 4,725 adults (18-59y), that provided data in routine health evaluations of a hospital in Brazil, followed for a mean period of 3.1±1.6 years. Physical activity, alcohol consumption (measured using Alcohol Use Disorders Identification Test) and tobacco smoking were categorized as: (1) absence of the behavior (inactivity i.e. not complying with 150 min of moderate-to-vigorous PA/week, not smoking, no risky drinking, i.e. AUDIT<5) during baseline and follow-up; (2) Absence during baseline and presence during follow-up; (3) Presence during baseline and absence during follow-up; (4) Presence during both time points. Depressive symptoms were measured with the Beck Inventory was adopted to analyze patterns of depressive symptoms over time (as exposure). C-reactive protein [HS-CRP]) was assessed and its role in the association was tested. Incidence indicators of behaviors and depressive symptoms were created and used as outcomes. We used crude and adjusted Poisson regression analysis.
Results: Fully adjusted models revealed that persistently physical inactive participants (RR:1.71;95%CI:1.33-2.21), those who became physically inactive (1.68;1.19-2.26), with consistently risky drinking (1.62;1.15-2.30), and who became risky drinkers (1.62;1.15-2.30) had higher risk for incidence of elevated depressive symptoms. Vice versa participants with incidence of depressive symptoms over time presented higher risk for physical inactivity (1.44;1.11-1.87) and risky drinking (1.65;1.16-2.34) incidence. HS-CRP did not influence the associations.
Limitations: Self-reported physical activity, binary tobacco smoking, and non-probabilistic sampling.
Conclusions: There is a prospective relationship between elevated depressive symptoms and adverse lifestyle behaviors.
Keywords
Exercise, smoking, depression, inflammation, physical activity, lifestyle

Introduction

Depression is one of the most important causes of disability worldwide (World Health Organization, 2017). Previous estimates found a prevalence of 4.4% for depression among adults, with women having a higher prevalence than men (5.5% vs. 3.2%) (World Health Organization, 2017). Depression reduces life expectancy by approximately 10 years (Chang et al., 2011), partly due to an increased risk for cardiovascular diseases (Correll et al., 2017; Firth et al., 2019; Swaraj et al., 2019). There are different mechanisms partly explaining the co-morbidity between depression and cardiovascular disease (Firth et al., 2019). Therefore, the adoption of different health behaviors (i.e., physical activity, not smoking and the non-elevated consumption of alcohol) can protect people with depression of developing chronic diseases (Firth et al., 2019).

Previous cross-sectional and longitudinal studies have demonstrated that unhealthy lifestyle behaviors such as physical inactivity, risky alcohol consumption and tobacco smoking are associated with the presence of elevated depressive symptoms in adults (An and Xiang, 2015; Fluharty et al., 2017; Schuch et al., 2018). However, the direction of the association (i.e., whether health behaviors predict depressive symptoms or vice versa) is less clear. There is a suggestion however that the associations of physical inactivity, tobacco smoking and risky alcohol consumption with depressive symptoms may be bidirectional (An and Xiang, 2015; Azevedo Da Silva et al., 2012; Choi et al., 2019; Firth et al., 2019; J. Firth et al., 2020; Fluharty et al., 2017; Kuo et al., 2010; Pacek et al., 2013).

Among the mechanisms linking multiple lifestyle behaviors and depression, one mechanism of interest is inflammation, since individuals with depression are known to have increased low-grade systemic inflammation (Köhler et al., 2017) as well as

lifestyle behaviors including physical inactivity, smoking and excessive alcohol consumption have also been associated with low-grade systemic inflammation (Fernandes et al., 2018; Mandrekar et al., 2009; Nunes et al., 2012). Therefore, low-grade systemic inflammation can confound or mediate the association between multiple lifestyle behaviors and depression. However, most studies testing the association of lifestyle behaviors with depression and depressive symptoms to date have not adjusted their findings for plasma HS-CRP concentrations or analyzed its role in the association.

There is also need for cohort studies investigating the association between lifestyle behaviors and depressive symptoms in middle-income countries (Schuch et al., 2018). Considering the marked inequalities in the adoption of health behaviors, together with the elevated prevalence of elevated depressive symptoms, it is possible that health behaviors can present distinct patterns in the association with health outcomes as depression (Arcaya et al., 2015; de Azevedo Barros et al., 2016; Munhoz et al., 2016). Therefore, the aim of this study was to analyze the interactions between lifestyle behaviors and the presence of elevated depressive symptoms over time in a large Brazilian cohort while exploring the influence of inflammatory biomarkers in this association.

Methods

Sample

The study included a non-probabilistic sample of Brazilian adults aged between 18 and 59 years old who participated in routine health evaluation at the Jardins unit of the Hospital Israelita Albert Einstein (São Paulo, Brazil) from January 2007 to December 2013. The study protocol was approved by the ethics committee of the local Institutional Review Board (Hospital Israelita Albert Einstein's ethics committee –

protocol number CAAE: 35855520.8.0000.0071), in compliance with the Brazilian National Research Ethics System Guidelines and the Ethical Guidelines of the 1975 Declaration of Helsinki. Originally, participants gave consent for the study and data were de-identified. Also, this specific study was waived to present informed consent, as it was a secondary analysis of an already existent database that had been approved for analysis. For the present study, we included all participants who underwent an initial visit within the program as well as had a follow-up visit with a minimum interval of one year.

The initial sample consisted of 8,195 adults (18-59 years) (6,579 men). After the exclusion of those with missing data and those presenting extreme outliers of HS-CRP due to infectious or inflammatory diseases (values > 10mg/L) (Pepys and Hirschfield, 2003), the final sample was composed of 4,725 adults. A flow-chart of study subjects is presented on **Figure 1**. To improve the identification of incident depressive symptoms or the multiple lifestyle factors during follow-up, those with the outcome present at baseline were excluded in those analyses (e.g., for physical inactivity incidence, participants with sufficient physical activity at baseline were excluded). Therefore, the final sample for each outcome was: Incidence of elevated depressive symptons: n = 4,032; Incidence of physical inactivity: n = 1,828; Incidence of tobacco smoking: n = 4,282; Incidence of risky alcohol consumption: n = 3,048.

Depressive symptoms

To assess the presence and severity of depressive symptoms, the Beck Depression Inventory (BDI) (Beck et al., 1986) was used. The questionnaire includes 21 Likert-scale questions about different depressive symptoms as sadness, anhedonia, lack of energy, sadness, feeling of guilt, sleep problems, among others. Based on previous

studies (Franco et al., 2017), we adopted the cutoff point of ≥10 to indicate the presence of depressive symptoms. This value is commonly used as a cutoff for the presence of at least mild symptoms in non-clinical samples (Wang and Gorenstein, 2013).

Lifestyle behaviors

The level of physical activity was assessed with the International Physical Activity Questionnaire (IPAQ), which contains questions related to leisure-time physical activity, occupational physical activity and transportation physical activity. The questionnaire is a good indicator of physical activity, particularly among leisure and occupational domains (Hallal et al., 2010). Participants with moderate to vigorous physical activity equal to or greater than 150 minutes in the week were classified as physically active in accordance with international recommendations (World Health Organization, 2020).

Tobacco smoking was assessed through a question about smoking habits "Do you usually smoke tobacco?" and the participants were classified as smokers or not smokers accordingly. Alcohol consumption was estimated through the Alcohol Use Disorders Identification Test (AUDIT) questionnaire and the cutoff point of 5 was adopted for risky alcohol consumption. This cutoff is commonly used in non-clinical samples (Meneses-Gaya et al., 2009).

Considering that we sought to investigate whether changes in the patterns of behaviors are associated with the incidence of elevated depressive symptoms and changes in the patterns of elevated depressive symptoms are associated with the incidence of behaviors, we classified physical activity, tobacco smoking and alcohol consumption in four groups: 1) absence of the behavior during baseline and follow-up; 2) Absence of the behavior during baseline and presence during follow-up; 3) Presence

of the behavior during baseline and absence during follow-up; 4) Presence of the behavior during both time points. For the association between patterns of depressive symptoms over time and incidence of lifestyle behaviors, we used incidence of each behavior, excluding participants with the presence of behaviors during baseline: Incidence of physical inactivity: 1- Participants meeting the physical activity recommendations in both baseline and follow-up, 2- Participants with recommended physical activity at the baseline, but not meeting the recommendations at the follow-up; Incidence of risky alcohol consumption: 1- Participants with adequate alcohol consumption in both baseline and follow-up, 2- Participants with adequate alcohol consumption at baseline, but risky alcohol consumption during the follow-up; Incidence of tobacco smoking: 1- Not smoking in both baseline and follow-up, 2- Not smoking at the baseline, but smoke at the follow-up.

HS-CRP

Plasma HS-CRP was determined by a turbidimetric method on a nephelometry system (Dade-Boehring, EUA) and the change between the first and the second wave was used. Considering that the presence of acute infections and inflammatory diseases can increase the HS-CRP and our aim was to evaluate the role of a chronically increased HS-CRP, we excluded extreme outliers of HS-CRP (values > 10mg/L) (Pepys and Hirschfield, 2003).

Covariates

Time between visits, sex, chronological age, number of metabolic risk factors, and self-rated health were used as covariates. We considered the components of metabolic syndrome as metabolic risk factors (i.e., waist circumference, blood pressure, fasting

glucose, triglycerides and HDL-cholesterol). Blood samples were collected after at least 12-hours fasting. Standardized laboratory analyses with commercial validated kits, including a standard lipid panel and fasting glucose were evaluated in the automated equipment VITROS 5600® Ortho Clinical Diagnostics by dry chemical colorimetric method. Waist circumference, a marker of central adiposity (measured in centimeters), was measured by placing a non-elastic measuring tape in a horizontal plane around a participant's bare abdomen at the top of the iliac crest as recommended, the participants were measured twice and a third assessment of waist circumference was taken in case of discrepancy between the two first measures. The cut-off points for the metabolic risk factors were according to the Adult Treatment Panel III (ATP III) (i.e. waist circumference ≥102 cm among men or ≥88cm among women; triglycerides ≥150 mg/dL; HDL-Cholesterol <40 mg/dL among men or <50 mg/dL among women; systolic blood pressure ≥130 mmHg and/or diastolic arterial blood pressure ≥85 mmHg; and glucose ≥100 mg/dL) (Grundy et al., 2005). Self-rated health was assessed through the 4-item Likert question: "In general, how do you evaluate your health?" with possible answers: A) "excellent", B) "good", C) "regular" or D) "bad". We considered those with excellent or good self-rated health as with good self-rated health.

Statistical procedures

Characteristics of sample were described using values of absolute frequencies, relative frequencies, means and standard deviations as well as median and interquartile range for HS-CRP. We adopted the strategy of investigating the incidence of the outcome and patterns of change in the exposure as it increases the causality interpretation. For the association between patterns of lifestyle behaviors over time and incidence of elevated depressive symptoms as well as for the association between patterns of depressive

symptoms over time and incidence of lifestyle behaviors, we used Poisson regression analysis with risk ratio (RR) and 95% confidence intervals (CI), including three models: Model 1: adjusted for time between visits, sex, chronological age; Model 2: Model 1 + number of metabolic risk factors and self-rated health. Model 3: Model 2 + changes in HS-CRP. To investigate the role of HS-CRP in the association of multiple health behaviors and incidence of depression and vice-versa, we conducted mediation models. Considering the mediation assumptions, we previously tested for the association between the exposure and mediator as well as between the mediator and outcome (Valeri and VanderWeele, 2013). As there was no association of the mediator with the lifestyle behaviors, we included HS-CRP as an adjustment factor in the analyzes. We have also conducted cross-lagged panel models using generalized structural equation models to assess the bidirectional association between the lifestyle behaviors and elevated depressive symptoms. All the analyses were conducted during the second semester of 2020, using the software Stata 15.1.

Results

Characteristics of study sample are presented on **Table 1**. The mean age of participants was 41.2 ± 7.9 years, and most were male (81%). During a mean follow-up of 3.1±1.6 years 468 (11.3%) participants presented incidence of elevated depressive symptoms while 587 (31.3%) became physically inactive, 100 (2.3%) started tobacco smoking, and 311 (9.9%) developed risky alcohol drinking patterns.

The associations between lifestyle behaviors and depressive symptoms are presented in **Tables 2 and 3**. Consistently inactive participants [RR: 1.71 (95%CI: 1.33 to 2.21)] as well as those who became inactive [RR: 1.68 (95%CI: 1.19 to 2.26)] over

time showed higher incidence of elevated depressive symptoms comparing with their consistently active peers. In opposition, participants with consistently elevated depressive symptoms [RR: 1.59 (95%CI: 1.18 to 2.15)] as well as participants without the presence of elevated depressive symptoms at baseline that evolved to elevated depressive symptoms at follow-up [RR: 1.44 (95%CI: 1.11 to 1.87)] were associated with higher risk for the incidence of physical inactivity comparing with those with consistently normal depressive symptoms.

Similarly, participants with consistent risky alcohol drinking [RR: 1.64 (95%CI: 1.31 to 2.05)] as well as those who become with risky alcohol drinking over time [RR: 1.62 (95%CI: 1.15 to 2.30)] were more likely to demonstrate elevated depressive symptoms comparing with those participants without risky alcohol drinking in both baseline and follow-up. Considering patterns of elevated depressive symptoms as exposure and incidence of risky alcohol drinking as outcome, the incidence of elevated depressive symptoms was also associated with higher risk for risky alcohol consumption incidence [RR: 1.65 (95%CI: 1.16 to 2.34)].

Tobacco smoking patterns were not associated with the incidence of elevated depressive symptoms [Smoke / not smoke RR:1.38 (95%CI:0.91 to 2.11); Not smoke / smoke: RR:0.76 (95%CI:0.38 to 1.70); Consistently smoke: RR:1.27 (95%CI:0.87 to 1.86)]. However, the maintenance of elevated depressive symptoms over time was associated with higher risk of tobacco smoking incidence [RR: 2.28 (95%CI: 1.26 to 4.10)], comparing with participants with consistently normal depressive symptoms.

While there was a reduction in the association between the behaviors and the incidence of elevated depressive symptoms from the model 1 to the model 2, the inclusion of HS-CRP did not affect the models, even HS-CRP change being associated with the incidence of elevated depressive symptoms in the models of physical activity

and alcohol consumption. In the other hand, HS-CRP change was not associated with the incidence of lifestyle behaviors.

The cross-lagged panel models supported the bidirectional association between physical activity practice and elevated depressive symptoms. Also, there was no association between tobacco smoking and elevated depressive symptoms. On the other hand, there was an association of elevated alcohol consumption predicting later elevated depressive symptoms, while elevated depressive symptoms did not predict risky alcohol consumption (**Supplementary Table A**).

Discussion

Our aim was to investigate the prospective association between multiple behaviors and depressive symptoms in a middle-income country as well as by adjusting the association between lifestyle behaviors and depressive symptoms for a low-grade systemic inflammation biomarker. Our main findings were that adults with consistent physical inactivity and risky alcohol consumption in both time-points and those who became physically inactive and risky alcohol drinkers over time showed higher risk for elevated depressive symptoms compared to their counterparts with consistently healthy habits. Moreover, consistently elevated depressive symptoms were associated with a higher incidence of physical inactivity and tobacco smoking. At the same time participants without depressive symptoms during baseline, but who developed depressive symptoms at follow-up showed lower risk for sufficient physical activity and higher risk for risky alcohol drinking. The cross-lagged panel suggested a bidirectional association between physical activity and elevated depressive symptoms, while alcohol consumption was prospectively associated with elevated depressive symptoms (but not *vice* versa) and there was no association between tobacco smoking and elevated depressive symptoms.

These findings were independent of potential confounders such as demographics and we found no evidence supporting a mediating role of HS-CRP.

Among the individual lifestyle factors we found that risky alcohol consumption can predict elevated depressive symptoms, but the opposite was not consistent in the cross-lagged models, supporting the close relationship between depressive symptoms and alcohol use disorders, especially with alcohol disorders being prospectively associated with elevated depressive symptoms (An and Xiang, 2015; Cabello et al., 2017). Several pathways can explain the association between risky alcohol use and depressive symptoms. First, the quality of life of risky drinkers is reduced, especially reporting pain/discomfort, impairment in mobility and in performing usual activities (Foster et al., 1999; Kim and Kim, 2015), which can be associated with depressive feelings. Second, there is evidence for a common genetic predisposition for risky drinking and depression (Kuo et al., 2010). Third, risky alcohol drinking can lead to neuro-immunological alterations, which are also associated with depressive symptoms (Archer et al., 2019). For example, chronic ethanol use is also proposed to upregulate transcription factor NF-κB (Nuclear factor-κB), causing immune cells in the periphery as well as glial cells in the central nervous system to produce pro-inflammatory cytokines (Mandrekar et al., 2009).

We also found that the participants that were consistently inactive or become inactive over time presented higher incidence of elevated depressive symptoms, which is also consistent with previous findings (Azevedo Da Silva et al., 2012; Choi et al., 2019). This association could be explained by several mechanisms. Even our findings were adjusted for HS-CRP, which is an indicator of low-grade systemic inflammation, it is also possible that other biological mechanisms can mediate this association. For example, other biological pathways that could explain the complex associations

between physical inactivity and elevated depressive symptoms are increases in IL-6, decreases in IL-10 release, changes in immunological markers produced by monocytes and macrophages (e.g. IL-1α, IL-1β and TNF-α), alterations in hippocampal volume and in neurotrophic factors (e.g. BDNF) (Firth et al., 2020; Howren et al., 2009; Kandola et al., 2019; Paolucci et al., 2018; Schuch et al., 2016). Moreover, social and psychological factors, such as social support, loneliness and the level of self-efficacy can mediate the association between physical activity and depressive symptoms (Hallgren et al., 2017; Kang et al., 2018; Matz-Costa et al., 2016). On the other hand, lower engagement in physical activity by people with depression was previously reported (Vancampfort et al., 2017), and has been explained by several perceived barriers for physical activity, such as low mood state and lack of energy, frequently observed among people with depression (Firth et al., 2016; Glowacki et al., 2017).

Tobacco smoking was not associated with risk for elevated depressive symptoms. Interestingly, the majority of previous evidence on the association between tobacco smoking and depressive symptoms was found in studies using longer follow-up periods compared to the present study, suggesting that a longer exposure to this behavior could be necessary to increase depressive symptoms (Fluharty et al., 2017). Another possible explanation for the null association can the binary indicator of tobacco smoking (yes or not), as previous studies found a dose-response association between tobacco smoking and depression (Matta et al., 2020; Vulser et al., 2015).

An interesting finding was that contrary to our hypothesis, HS-CRP did not have any influence in the analyzes. Different factors can explain this association. First, it is possible that participants who started to present the outcomes already had a higher HS-CRP value at baseline and, consequently, the change in HS-CRP over time was not significant. For example, even HS-CRP change not influencing the associations, it was

inversely associated with the incidence of elevated depressive symptoms, which can possibly indicate that the participants with incident elevated depressive symptoms likely presented higher HS-CRP during the baseline and therefore, they tended to present a slightly reduction over time. Furthermore, it is possible that other possible mechanisms, including biological, psychological and social factors, as previously presented, have a greater power to explain the association than HS-CRP (Kandola et al., 2019; Mandrekar et al., 2009). Even though HS-CRP change is an indicator of systemic inflammation, it is possible that other uncontrolled inflammatory markers may mediate part of the association, such as alterations and cytokines, such as IL-6.

Our findings highlight that appropriate treatment for participants with elevated depressive symptoms should be include interventions targeting behavioral risk factors (Firth et al., 2019). Given the wider adverse health outcomes from low physical activity, smoking and increased alcohol consumption (Han et al., 2019; Lee et al., 2012; Sinha et al., 2018), the potential impact of these factors being adversely impact in participants with depressive symptoms are concerning. Therefore, interventions focusing on reducing risky alcohol consumption, and increasing physical activity can be effective in reducing depressive symptoms. Such efforts to improve these factors in those presenting with depressive symptoms are also primordial to increase the quality of life and protect physical health (Ashdown-Franks et al., 2020; Firth et al., 2019; Gates et al., 2015; Gilbody et al., 2019; Rüther et al., 2014).

Our results should be interpreted in the light of some limitations. First, this study included a non-probabilistic sample, and the extrapolation should be made with caution. Second, physical activity was self-reported, which can present a potential bias when compared with objective/device-based methods, as accelerometers. Third, we only included a single binary question regarding tobacco smoking, which can limit the

comprehension of its association with depressive symptoms as the association can be potentially dose-dependent (Matta et al., 2020; Vulser et al., 2015). Fourth, we were unable to adjust for employment status, socioeconomic status and sedentary behavior, which are all associated with depressive symptoms and the lifestyle behaviors (Werneck et al., 2018). Therefore, it is possible that the coefficients are overestimated. Fifth, data were only available for two time-points (baseline and follow up), limiting the inference of more detailed longitudinal patterns in the lifestyle behaviors and depressive symptoms. Sixth, we only conducted one measurement of waist circumference, which can represent a bias. On the other hand, we provide longitudinal data from a middle-income country investigating the association between lifestyle behaviors and depressive symptoms, also exploring the role of HS-CRP.

Conclusions

The current study demonstrates that depressive symptoms patterns can be prospectively associated with the adoption of physical inactivity, while vice versa the adoption of unhealthy behaviors can be prospectively associated with depressive symptoms. These findings highlight the importance of preventive interventions aiming to reduce risky alcohol consumption and improve physical activity levels and addressing depressive symptoms to prevent future unhealthy behaviors from developing.

Author contribution

AOW, GGC, DGDC, RDS, RMRD and MSB contributed to the conception and design of the work AOW, DGDC, GGC, RDS, RMRD and MSB contributed to the acquisition, analysis, or interpretation of data for the work. AOW drafted the manuscript. DV, BS, DRS, GGC, RDS, RMRD and MSB critically revised the manuscript. All authors gave

final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest

RDS has received honoraria related to consulting, research and or speaker activities from: Abbott, Amgen, Aché, Astra Zeneca, EMS, Esperion, Getz Pharma, Kowa, Libbs, Merck, Novartis, Novo-Nordisk, PTC, Pfizer, and Sanofii/Regeneron. Other authors have nothing to disclose.

Acknowledgement

We gratefully thank all the staff involved in the collection of data.

Compliance with ethical standards

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. AW is supported by the São Paulo Research Foundation (FAPESP) with a PhD scholarship (FAPESP process: 2019/24124-7). RDS is a recipient of a scholarship from the Conselho Nacional de Pesquisa e Desenvolvimento Tecnologico (CNPq) process # 303734/2018-3, Brazil. This paper presents independent research. The views expressed in this publication are those of the authors and not necessarily those of the acknowledged institutions.

Ethics approval

All procedures performed in the original studies involving human participants were approved by the local ethics committee in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

An, R., Xiang, X., 2015. Smoking, heavy drinking, and depression among U.S. middle-aged and older adults. Preventive Medicine 81, 295–302. https://doi.org/10.1016/j.ypmed.2015.09.026

Arcaya, M.C., Arcaya, A.L., Subramanian, S.V., 2015. Inequalities in health: definitions, concepts, and theories. Global Health Action 8, 27106. https://doi.org/10.3402/gha.v8.27106

Archer, M., Niemelä, O., Luoto, K., Kultti, J., Hämäläinen, M., Moilanen, E., Koivukangas, A., Leinonen, E., Kampman, O., 2019. Status of inflammation and alcohol use in a 6-month follow-up study of patients with major depressive disorder. Alcohol S0741832917309801. https://doi.org/10.1016/j.alcohol.2019.02.001

Ashdown-Franks, G., Firth, J., Carney, R., Carvalho, A.F., Hallgren, M., Koyanagi, A., Rosenbaum, S., Schuch, F.B., Smith, L., Solmi, M., Vancampfort, D., Stubbs, B., 2020. Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes. Sports Med 50, 151–170. https://doi.org/10.1007/s40279-019-01187-6

Azevedo Da Silva, M., Singh-Manoux, A., Brunner, E.J., Kaffashian, S., Shipley, M.J., Kivimäki, M., Nabi, H., 2012. Bidirectional association between physical activity and symptoms of anxiety and depression: the Whitehall II study. Eur J Epidemiol 27, 537–546. https://doi.org/10.1007/s10654-012-9692-8

Beck, A., Steer, R.A., Gk, B., 1986. Manual for the Beck depression inventory-II. Psychological Corporation, San Antonio, TX.

Cabello, M., Miret, M., Caballero, F.F., Chatterji, S., Naidoo, N., Kowal, P., D'Este, C., Ayuso-Mateos, J.L., 2017. The role of unhealthy lifestyles in the incidence and persistence of depression: a longitudinal general population study in four emerging countries. Global Health 13, 18. https://doi.org/10.1186/s12992-017-0237-5

Chang, C.-K., Hayes, R.D., Perera, G., Broadbent, M.T.M., Fernandes, A.C., Lee, W.E., Hotopf, M., Stewart, R., 2011. Life Expectancy at Birth for People with Serious Mental Illness and Other Major Disorders from a Secondary Mental Health Care Case Register in London. PLoS ONE 6, e19590. https://doi.org/10.1371/journal.pone.0019590

Choi, K.W., Chen, C.-Y., Stein, M.B., Klimentidis, Y.C., Wang, M.-J., Koenen, K.C., Smoller, J.W., for the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2019. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. JAMA Psychiatry 76, 399. https://doi.org/10.1001/jamapsychiatry.2018.4175

Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 16, 163–180. https://doi.org/10.1002/wps.20420

de Azevedo Barros, M.B., Lima, M.G., Medina, L. de P.B., Szwarcwald, C.L., Malta, D.C., 2016. Social inequalities in health behaviors among Brazilian adults: National Health Survey, 2013. Int J Equity Health 15, 148. https://doi.org/10.1186/s12939-016-0439-0

Fernandes, R.A., Ritti-Dias, R.M., Balagopal, P.B., Conceição, R.D.O., Santos, R.D., Cucato, G.G., Bittencourt, M.S., 2018. Self-initiated physical activity is associated with high sensitivity C-reactive protein: A longitudinal study in 5,030 adults. Atherosclerosis 273, 131–135. https://doi.org/10.1016/j.atherosclerosis.2018.02.011

Firth, J., Rosenbaum, S., Stubbs, B., Gorczynski, P., Yung, A.R., Vancampfort, D., 2016. Motivating factors and barriers towards exercise in severe mental illness: a systematic review and meta-analysis. Psychological Medicine 46, 2869–2881. https://doi.org/10.1017/S0033291716001732

Firth, J., Siddiqi, N., Koyanagi, A., Siskind, D., Rosenbaum, S., Galletly, C., Allan, S., Caneo, C., Carney, R., Carvalho, A.F., Chatterton, M.L., Correll, C.U., Curtis, J., Gaughran, F., Heald, A., Hoare, E., Jackson, S.E., Kisely, S., Lovell, K., Maj, M., McGorry, P.D., Mihalopoulos, C., Myles, H., O'Donoghue, B., Pillinger, T., Sarris, J., Schuch, F.B., Shiers, D., Smith, L., Solmi, M., Suetani, S., Taylor, J., Teasdale, S.B., Thornicroft, G., Torous, J., Usherwood, T., Vancampfort, D., Veronese, N., Ward, P.B., Yung, A.R., Killackey, E., Stubbs, B., 2019. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. The Lancet Psychiatry 6, 675–712. https://doi.org/10.1016/S2215-0366(19)30132-4

Firth, J., Solmi, M., Wootton, R.E., Vancampfort, D., Schuch, F.B., Hoare, E., Gilbody, S., Torous, J., Teasdale, S.B., Jackson, S.E., Smith, L., Eaton, M., Jacka, F.N., Veronese, N., Marx, W., Ashdown-Franks, G., Siskind, D., Sarris, J., Rosenbaum, S., Carvalho, A.F., Stubbs, B., 2020. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry 19, 360–380. https://doi.org/10.1002/wps.20773

Firth, J.A., Smith, L., Sarris, J., Vancampfort, D., Schuch, F., Carvalho, A.F., Solmi, M., Yung, A.R., Stubbs, B., Firth, J., 2020. Handgrip Strength Is Associated With Hippocampal Volume and White Matter Hyperintensities in Major Depression and Healthy Controls: A UK Biobank Study. Psychosomatic Medicine 82, 39–46. https://doi.org/10.1097/PSY.0000000000000753

Fluharty, M., Taylor, A.E., Grabski, M., Munafò, M.R., 2017. The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review. Nicotine & Tobacco Research 19, 3–13. https://doi.org/10.1093/ntr/ntw140

Foster, J.H., Powell, J.E., Marshall, E.J., Peters, T.J., 1999. Quality of Life in alcohol-dependent subjects - a review. Qual Life Res 8, 255–61.

Franco, F.G. de M., Laurinavicius, A.G., Lotufo, P.A., Conceição, R.D., Morita, F., Katz, M., Wajngarten, M., Carvalho, J.A.M., Bosworth, H.B., Santos, R.D., 2017. Persistent Depressive Symptoms are Independent Predictors of Low-Grade Inflammation Onset Among Healthy Individuals. Arquivos Brasileiros de Cardiologia. https://doi.org/10.5935/abc.20170080

Gates, J., Killackey, E., Phillips, L., Álvarez-Jiménez, M., 2015. Mental health starts with physical health: current status and future directions of non-pharmacological interventions to improve physical health in first-episode psychosis. The Lancet Psychiatry 2, 726–742. https://doi.org/10.1016/S2215-0366(15)00213-8

Gilbody, S., Peckham, E., Bailey, D., Arundel, C., Heron, P., Crosland, S., Fairhurst, C., Hewitt, C., Li, J., Parrott, S., Bradshaw, T., Horspool, M., Hughes, E., Hughes, T., Ker, S., Leahy, M., McCloud, T., Osborn, D., Reilly, J., Steare, T., Ballantyne, E., Bidwell, P., Bonner, S., Brennan, D., Callen, T., Carey, A., Colbeck, C., Coton, D., Donaldson, E., Evans, K., Herlihy, H., Khan, W., Nyathi, L., Nyamadzawo, E., Oldknow, H., Phiri, P., Rathod, S., Rea, J., Romain-Hooper, C.-B., Smith, K., Stribling, A., Vickers, C., 2019. Smoking cessation for people with severe

mental illness (SCIMITAR+): a pragmatic randomised controlled trial. The Lancet Psychiatry 6, 379–390. https://doi.org/10.1016/S2215-0366(19)30047-1

Glowacki, K., Duncan, M.J., Gainforth, H., Faulkner, G., 2017. Barriers and facilitators to physical activity and exercise among adults with depression: A scoping review. Mental Health and Physical Activity 13, 108–119. https://doi.org/10.1016/j.mhpa.2017.10.001

Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., Gordon, D.J., Krauss, R.M., Savage, P.J., Smith, S.C., Spertus, J.A., Costa, F., 2005. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112, 2735–2752. https://doi.org/10.1161/CIRCULATIONAHA.105.169404

Hallal, P.C., Gomez, L.F., Parra, D.C., Lobelo, F., Mosquera, J., Florindo, A.A., Reis, R.S., Pratt, M., Sarmiento, O.L., 2010. Lessons Learned After 10 Years of IPAQ Use in Brazil and Colombia. Journal of Physical Activity and Health 7, S259–S264. https://doi.org/10.1123/jpah.7.s2.s259

Hallgren, M., Lundin, A., Tee, F.Y., Burström, B., Forsell, Y., 2017. Somebody to lean on: Social relationships predict post-treatment depression severity in adults. Psychiatry Research 249, 261–267. https://doi.org/10.1016/j.psychres.2016.12.060

Han, T., Zhang, S., Duan, W., Ren, X., Wei, C., Sun, C., Li, Y., 2019. Eighteen-year alcohol consumption trajectories and their association with risk of type 2 diabetes and its related factors: the China Health and Nutrition Survey. Diabetologia 62, 970–980. https://doi.org/10.1007/s00125-019-4851-z

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. Psychosomatic Medicine 71, 171–186.

Kandola, A., Ashdown-Franks, G., Hendrikse, J., Sabiston, C.M., Stubbs, B., 2019. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. Neuroscience & Biobehavioral Reviews 107, 525–539. https://doi.org/10.1016/j.neubiorev.2019.09.040

Kang, H.-W., Park, M., Wallace (Hernandez), J.P., 2018. The impact of perceived social support, loneliness, and physical activity on quality of life in South Korean older adults. Journal of Sport and Health Science 7, 237–244. https://doi.org/10.1016/j.jshs.2016.05.003

Kim, K., Kim, J.-S., 2015. The Association between Alcohol Consumption Patterns and Health-Related Quality of Life in a Nationally Representative Sample of South Korean Adults. PLoS ONE 10, e0119245. https://doi.org/10.1371/journal.pone.0119245

Köhler, C.A., Freitas, T.H., Maes, M., de Andrade, N.Q., Liu, C.S., Fernandes, B.S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C.L., Miller, B.J., Lanctôt, K.L., Carvalho, A.F., 2017. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatrica Scandinavica 135, 373–387. https://doi.org/10.1111/acps.12698

Kuo, P.-H., Neale, M.C., Walsh, D., Patterson, D.G., Riley, B., Prescott, C.A., Kendler, K.S., 2010. Genome-wide linkage scans for major depression in individuals

with alcohol dependence. Journal of Psychiatric Research 44, 616–619. https://doi.org/10.1016/j.jpsychires.2009.12.005

Lee, I.-M., Shiroma, E.J., Lobelo, F., Puska, P., Blair, S.N., Katzmarzyk, P.T., 2012. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The Lancet 380, 219–229. https://doi.org/10.1016/S0140-6736(12)61031-9

Mandrekar, P., Bala, S., Catalano, D., Kodys, K., Szabo, G., 2009. The Opposite Effects of Acute and Chronic Alcohol on Lipopolysaccharide-Induced Inflammation Are Linked to IRAK-M in Human Monocytes. J Immunol 183, 1320–1327. https://doi.org/10.4049/jimmunol.0803206

Matta, J., Hoertel, N., Airagnes, G., Wiernik, E., Limosin, F., Goldberg, M., Zins, M., Lemogne, C., 2020. Does substance use explain social differences in terms of depression? Findings from the Constances cohort. Comprehensive Psychiatry 102, 152203. https://doi.org/10.1016/j.comppsych.2020.152203

Matz-Costa, C., Carr, D.C., McNamara, T.K., James, J.B., 2016. Physical, Cognitive, Social, and Emotional Mediators of Activity Involvement and Health in Later Life. Res Aging 38, 791–815. https://doi.org/10.1177/0164027515606182

Meneses-Gaya, C., Zuardi, A.W., Loureiro, S.R., Crippa, J.A.S., 2009. Alcohol Use Disorders Identification Test (AUDIT): An updated systematic review of psychometric properties. Psychology & Neuroscience 2, 83–97. https://doi.org/10.3922/j.psns.2009.1.12

Munhoz, T.N., Nunes, B.P., Wehrmeister, F.C., Santos, I.S., Matijasevich, A., 2016. A nationwide population-based study of depression in Brazil. Journal of Affective Disorders 192, 226–233. https://doi.org/10.1016/j.jad.2015.12.038

Nunes, S.O.V., Vargas, H.O., Brum, J., Prado, E., Vargas, M.M., Castro, M.R.P. d., Dodd, S., Berk, M., 2012. A Comparison of Inflammatory Markers in Depressed and Nondepressed Smokers. Nicotine & Tobacco Research 14, 540–546. https://doi.org/10.1093/ntr/ntr247

Pacek, L.R., Martins, S.S., Crum, R.M., 2013. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: Results from a national sample. Journal of Affective Disorders 148, 188–195. https://doi.org/10.1016/j.jad.2012.11.059

Paolucci, E.M., Loukov, D., Bowdish, D.M.E., Heisz, J.J., 2018. Exercise reduces depression and inflammation but intensity matters. Biological Psychology 133, 79–84. https://doi.org/10.1016/j.biopsycho.2018.01.015

Pepys, M.B., Hirschfield, G.M., 2003. C-reactive protein: a critical update. J. Clin. Invest. 111, 1805–1812. https://doi.org/10.1172/JCI200318921

Rüther, T., Bobes, J., De Hert, M., Svensson, T.H., Mann, K., Batra, A., Gorwood, P., Möller, H.J., 2014. EPA Guidance on Tobacco Dependence and Strategies for Smoking Cessation in People with Mental Illness. Eur. psychiatr. 29, 65–82. https://doi.org/10.1016/j.eurpsy.2013.11.002

Schuch, F.B., Deslandes, A.C., Stubbs, B., Gosmann, N.P., Silva, C.T.B. da, Fleck, M.P. de A., 2016. Neurobiological effects of exercise on major depressive disorder: A systematic review. Neuroscience & Biobehavioral Reviews 61, 1–11. https://doi.org/10.1016/j.neubiorev.2015.11.012

Schuch, F.B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P.B., Silva, E.S., Hallgren, M., Ponce De Leon, A., Dunn, A.L., Deslandes, A.C., Fleck, M.P., Carvalho, A.F., Stubbs, B., 2018. Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. American Journal of Psychiatry 175, 631–648. https://doi.org/10.1176/appi.ajp.2018.17111194

Sinha, D.N., Suliankatchi, R.A., Gupta, P.C., Thamarangsi, T., Agarwal, N., Parascandola, M., Mehrotra, R., 2018. Global burden of all-cause and cause-specific mortality due to smokeless tobacco use: systematic review and meta-analysis. Tobacco Control 27, 35–42.

Swaraj, S., Chung, D., Curtis, J., Firth, J., Ramanuj, P.P., Sara, G., Wang, M., Large, M., 2019. Meta-analysis of Natural, Unnatural, and Cause-Specific Mortality Rates Following Discharge From Inpatient Psychiatric Facilities. Acta Psychiatrica Scandinavica. https://doi.org/10.1111/acps.13073

Valeri, L., VanderWeele, T.J., 2013. Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. Psychological Methods 18, 137–150. https://doi.org/10.1037/a0031034

Vancampfort, D., Firth, J., Schuch, F.B., Rosenbaum, S., Mugisha, J., Hallgren, M., Probst, M., Ward, P.B., Gaughran, F., De Hert, M., Carvalho, A.F., Stubbs, B., 2017. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. World Psychiatry 16, 308–315. https://doi.org/10.1002/wps.20458

Vulser, H., Wiernik, E., Tartour, E., Thomas, F., Pannier, B., Czernichow, S., Hanon, O., Simon, T., Simon, J.-M., Ducolombier, C., Consoli, S.M., Danchin, N., Limosin, F., Lemogne, C., 2015. Smoking and the Association Between Depressive Symptoms and Absolute Neutrophil Count in the Investigations Préventives et Cliniques Cohort Study. Psychosomatic Medicine 77, 1039–1049. https://doi.org/10.1097/PSY.0000000000000243

Wang, Y.-P., Gorenstein, C., 2013. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Revista Brasileira de Psiquiatria 35, 416–431. https://doi.org/10.1590/1516-4446-2012-1048

Werneck, A.O., Oyeyemi, A.L., Szwarcwald, C.L., Vancampfort, D., Silva, D.R., 2018. Associations between TV viewing and depressive symptoms among 60,202 Brazilian adults: The Brazilian national health survey. Journal of Affective Disorders 236, 23–30. https://doi.org/10.1016/j.jad.2018.04.083

World Health Organization, 2020. WHO guidelines on physical activity and sedentary behaviour. World Health Organization, Geneva, Switzerland.

World Health Organization, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization, Geneva.

Figure Legend

Figure 1. Study subjects flow chart.

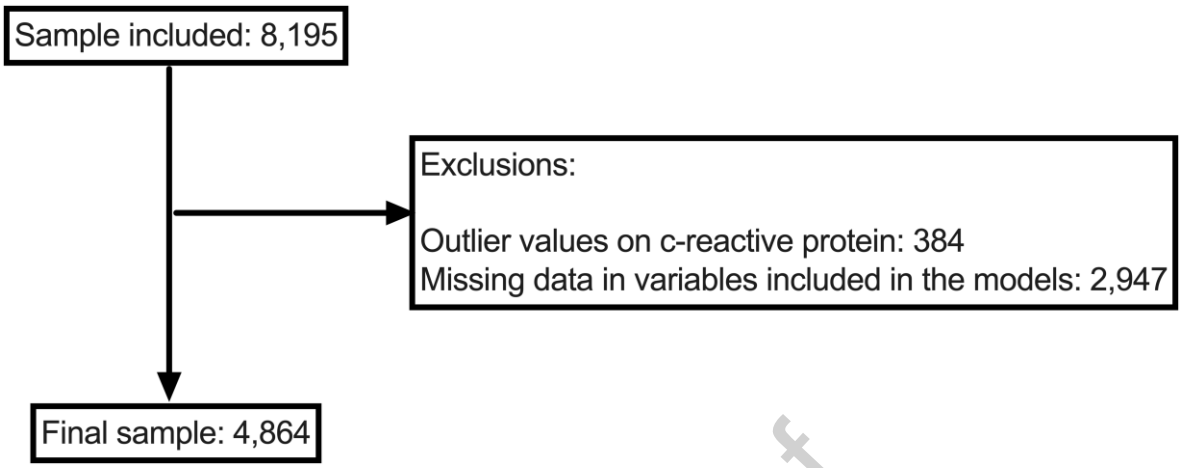

Table 1. Clinical and laboratory characteristics of sample (n=4,725).

Variable	Categories	
Sex (men)		3,814 (80.7)
Chronological age, y		41.2 ± 7.9
Time between visits, y		3.1 ± 1.6
Elevated waist circumference (%)		1,091 (23.1)
Elevated blood pressure (%)		1,038 (22.0)
Elevated fasting glucose (%)		144 (3.1)
Elevated triglycerides (%)		1,416 (30.0)
Low HDL-Cholesterol (%)		1,400 (29.6)
Number of metabolic risk factors (n)		0.85 ± 1.0
HS-CRP, baseline in mg/L		1.1 (0.6 - 2.1)
HS-CRP, follow-up in mg/L		1.0 (0.5 - 2.1)
HS-CRP, change in mg/L		0.0 (0 - 0)
Self-rated health (good)		4,472 (94.7)
Physical activity patterns		
	Consistently active, %	1,256 (26.4)
	Inactive / Active, %	974 (20.6)
	Active / Inactive, %	573 (12.1)
	Consistently inactive, %	1,922 (40.9)
Tobacco smoking patterns		
	Consistently not smoke, %	4,187 (88.4)
	Smoking/Not smoke, %	181 (3.9)
	Not smoking/smoke, %	97 (2.1)
	Consistently smoke, %	260 (5.6)
Alcohol consumption patterns		
	Consistently low, %	2,751 (58.2)
	Elevated/Low, %	562 (11.9)
	Low/Elevated, %	299 (6.3)
	Consistently Elevated, %	1,113 (23.6)
Depressive symptoms		
	Consistently normal, %	3,579 (75.8)
	Elevated/normal, %	330 (7.0)
	Normal/Elevated, %	454 (9.6)
	Consistently elevated, %	362 (7.6)
Incidence during follow-up		
Elevated DS*(%)		454 (11.3)
Physical inactivity** (%)		573 (31.3)
Tobacco smoking***(%)		97 (2.3)
Risky alcohol consumption**** (%)		299 (9.8)

Note. Values are presented using values of absolute frequencies (relative frequencies), mean and standard deviations for chronological age and time between visits or median and interquartile range for high sensitivity C-reactive protein. DS, depressive symptoms. HS-CRP, high sensitivity C-reactive protein. *n: 4,032. **n: 1,828. ***n: 4,282. ****n: 3,048. Elevated waist circumference refers to ≥102 cm for men and ≥88 cm for women. C-reactive protein values were presented using median and interquartile range.

Table 2. Association between patterns of lifestyle behaviors and incidence of elevated depressive symptoms along time.

	Models		
	Model 1 RR (95%CI)	**Model 2 RR (95%CI)**	**Model 3 RR (95%CI)**
Physical activity			
Consistently active	Ref	Ref	Ref
Inactive / Active	1.12 (0.82 to 1.53)	1.08 (0.79 to 1.48)	1.09 (0.80 to 1.49)
Active / Inactive	1.73 (1.26 to 2.39)	1.63 (1.18 to 2.25)	1.68 (1.19 to 2.26)
Consistently inactive	1.88 (1.46 to 2.41)	1.70 (1.32 to 2.19)	1.71 (1.33 to 2.21)
HS-CRP	-	-	0.94 (0.89-0.99)
Tobacco smoking			
Consistently not smoke	Ref	Ref	Ref
Smoke / Not smoke	1.39 (0.91 to 2.11)	1.40 (0.92 to 2.13)	1.38 (0.91 to 2.11)
Not smoke / smoke	0.89 (0.42 to 1.87)	0.79 (0.37 to 1.67)	0.76 (0.38 to 1.70)
Consistently smoke	1.33 (0.91 to 1.94)	1.27 (0.87 to 1.86)	1.27 (0.87 to 1.86)
HS-CRP	-	-	0.94 (0.89-1.00)
Alcohol consumption			
Consistently low	Ref	Ref	Ref
Elevated / Low	1.06 (0.77 to 1.45)	1.04 (0.76 to 1.44)	1.04 (0.76 to 1.43)
Low / Elevated	1.60 (1.14 to 2.27)	1.64 (1.16 to 2.32)	1.62 (1.15 to 2.30)
Consistently elevated	1.61 (1.29 to 2.02)	1.63 (1.30 to 2.05)	1.64 (1.31 to 2.05)
HS-CRP	-	-	0.94 (0.89-0.99)

Note. Model 1: Adjusted by time between visits, chronological age and sex. Model 2: Model 1 + number of metabolic risk factors and self-rated health. Model 3: Model 2 + HS-CRP. RR, risk ratio. CI, confidence interval. The models only included participants without elevated depressive symptoms during the baseline (n=4,032).

Table 3. Association between patterns of elevated depressive symptoms and incidence of lifestyle behaviors along time.

Depressive symptoms patterns	Models		
	Model 1 RR (95%CI)	**Model 2 RR (95%CI)**	**Model 3 RR (95%CI)**
Outcome: Physical inactivity			
Consistently normal	Ref	Ref	Ref
Elevated / normal	1.14 (0.78 to 1.64)	1.11 (0.76 to 1.61)	1.10 (0.76 to 1.60)
Normal / Elevated	1.50 (1.16 to 1.95)	1.43 (1.10 to 1.86)	1.44 (1.11 to 1.87)
Consistently elevated	1.82 (1.36 to 2.42)	1.62 (1.21 to 2.19)	1.59 (1.18 to 2.15)
HS-CRP	-	-	1.04 (0.98-1.10)
Outcome: Tobacco smoking			
Consistently normal	Ref	Ref	Ref
Elevated / normal	1.06 (0.46 to 2.45)	1.05 (0.45 to 2.42)	1.06 (0.46 to 2.44)
Normal / Elevated	0.87 (0.40 to 1.90)	0.83 (0.38 to 1.81)	0.84 (0.38 to 1.84)
Consistently elevated	2.59 (1.47 to 4.56)	2.31 (1.28 to 4.16)	2.28 (1.26 to 4.10)
HS-CRP	-	-	1.10 (0.97-1.24)
Outcome: Risky alcohol use			
Consistently normal	Ref	Ref	Ref
Elevated / normal	1.48 (0.97 to 2.26)	1.48 (0.97 to 2.26)	1.47 (0.96 to 2.25)
Normal / Elevated	1.63 (1.15 to 2.30)	1.65 (1.17 to 2.34)	1.65 (1.16 to 2.34)
Consistently elevated	1.30 (0.83 to 2.02)	1.39 (0.88 to 2.19)	1.39 (0.88 to 2.19)
HS-CRP	-	-	0.98 (0.91-1.05)

Note. Model 1: Adjusted by time between visits, chronological age. Model 2: Model 1 + number of metabolic risk factors and self-rated health. Model 3: Model 2 + HS-CRP. RR, risk ratio. CI, confidence interval. Models for physical inactivity only included those active during the baseline (n=1,828), models for tobacco smoking only included those without tobacco smoking during the baseline (n=4,282) and the models for risky alcohol use only included those without risky alcohol drinking during the baseline (n=3,048).