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Research paper

Mentally-passive sedentary behavior and incident depression: Mediation by inflammatory markers

André O. Werneck [a], Neville Owen [b,c], Raphael H.O. Araujo [d], Danilo R. Silva [e,f,g], Mats Hallgren [h,*]

[a] Center for Epidemiological Research in Nutrition and Health, Department of Nutrition, School of Public Health, Universidade de São Paulo (USP), Brazil
[b] Centre for Urban Transitions, Swinburne University of Technology, Hawthorn, Victoria, Australia
[c] Baker Heart & Diabetes Institute, Melbourne, Victoria, Australia
[d] Graduation Program in Health Sciences, Londrina State University (UEL), Londrina, Brazil
[e] Department of Physical Education, Federal University of Sergipe (UFS), São Cristóvão, Brazil
[f] Department of Sports and Computer Science, Universidad Pablo de Olavide (UPO), Seville, Spain
[g] Faculty of Health Sciences, Universidad Autónoma de Chile, Santiago, Chile
[h] Epidemiology of Psychiatric Conditions, Substance use and Social Environment (EPiCSS), Department of Global Public Health, Karolinska Institutet, Stockholm 171 77, Sweden

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ABSTRACT

Background: Sedentary behavior (SB; time spent sitting, as distinct from lack of exercise or physical activity) is associated with depression, yet little is known about the relationship between different types of SB (e.g., mentally-passive versus mentally-active) with depression and potential biological mediators of these associations.

Methods: We used cohort data from the 1958 National Child Development Study (n = 4607; 50.4 % women), conducted in UK, employing the 44 y and 46 y waves as baseline, and the 50 y and 55 y waves as follow-up. Participants reported time spent in TV viewing and watching videos (mentally-passive SB); and, time sitting while doing light activities such as deskwork or driving a car during worktime (mentally-active SB). Depression diagnosis was self-reported during the initial and follow-up waves. Waist circumference, C-reactive protein, and glycated hemoglobin were examined as potential mediators.

Results: Mentally-passive SB was associated with incident depression (HR: 1.43; 95%CI: 1.19; 1.71), while there was no association for mentally-active SB. Waist circumference (coefficient: −0.03; 95%CI: −0.05; −0.01; 9.2 %) and C-reactive protein (coefficient: −0.03; 95%CI: −0.04; −0.01; 8.3 %), but not glycated hemoglobin, partly mediated the association for mentally-passive SB.

Conclusions: In the relationship of mentally-passive SB with incident depression, the mediating contributions of waist circumference and C-reactive protein point to possible inflammatory-related mechanisms.

1. Introduction

Depression is a common disorder in adult populations with a global prevalence of approximately 4.4 % (95%CI: 4.1–4.7) in 2015, and is one of the leading causes of disability (World Health Organization, 2017). A broad understanding of risk and protective factors for depression is essential for the formulation of effective prevention strategies. There is role in depression of sedentary behavior, defined as any waking behavior while sitting, reclining or lying with an energy expenditure ≤1.5 metabolic equivalents (Tremblay et al., 2017). A meta-analysis including prospective studies found that higher total sedentary time was associated with a 10 % higher risk for developing depression (Huang et al., 2020). Furthermore, trials with induced sedentary behavior interventions during free-living activities have shown negative effects on mood states (Edwards and Loprinzi, 2016; Endrighi et al., 2016).

Sedentary behavior can be accumulated in different ways (e.g., watching TV, sitting during a work meeting, reading, watching a movie

* Corresponding author at: Epidemiology of Psychiatric Conditions, Substance Use and Social Environment (EPiCSS), Department of Global Public Health Sciences, Karolinska Institutet, Stockholm 171 77, Sweden.
E-mail address: mats.hallgren@ki.se (M. Hallgren).

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in the cinema, among others). The type and context (e.g., work/leisure) of sedentary behavior appears to influence the association with depression (Hallgren et al., 2018; Werneck et al., 2021). Based on this observation, and assumed differences in cognitive demand, a distinction has been proposed between sedentary behaviors that are mentally-passive (e.g., TV viewing) and those that are mentally-active (e.g., office work, reading) (Hallgren et al., 2020a). Studies have found mentally-passive sedentary behavior to be associated with a higher risk for depression, while mentally-active sedentary behavior was unrelated or even had a protective relationship with incident depression (Hallgren et al., 2018; Huang et al., 2020; Werneck et al., 2021). Although the findings of previous studies were consistent across different cohorts, the evidence on distinct associations of mentally-passive and mentally-active sedentary behavior with depression has limitations. The majority of observational studies have only assessed total sitting time, which could mask differential associations (Hallgren et al., 2020a).

In addition to further clarifying distinct associations of mentally-passive and mentally-active sedentary behavior with depression, understanding the role of potential mediators could reveal underlying mechanisms and help to provide a rational basis for future clinical and public health initiatives. While previous studies have shown that sleep quality and self-rated health partly explained the association of mentally-passive sedentary behavior with depression (Hallgren et al., 2020c; Werneck et al., 2021), there are other, biologically plausible, mediators of this association. Lower levels of sedentary behavior can be associated with reduced inflammation (Howard et al., 2015), lower blood glucose (Thorp et al., 2010), and lower body fat (Kikuchi et al., 2014). The potential roles of such biological mediators in the relationships of mentally-passive and mentally active sedentary behaviors with depression have not been investigated.

We examined prospective relationships of mentally-passive and mentally-active sedentary behaviors with incident depression, and the potential mediating roles of C-reactive protein, waist circumference and glycated hemoglobin.

2. Methods

2.1. Sample

The 1958 National Child Development Study (NCDS) is a cohort study that included all individuals from England, Scotland, Wales, and Northern Ireland who were born in a specific week of 1958. We included data from the 44 y (2002), 46 y (2005), 50 y (2008), and 55 y (2013) assessments. All the procedures were approved by the South East Multicentre Research Ethics Committee for the 44 y wave (01/1/44), by an internal ethics committee for the 46 y wave, by the London Multicentre Research Ethics Committee for the 50 y (08/H0718/29) waves, and by the London – Central (12/LO/2010) for the 55 y wave. Participants provided informed consent. The initial study sample consisted of 9377 with data at 44 y. However, 4253 participants did not answer any other prior wave or had missing data in at least one of the included variables, there were 367 prevalent cases of depression and 150 outlier values for C-reactive protein, which were excluded from the sample. Therefore, the final analytical sample included 4607 (2320 women). Details of the 1958 NCDS have been described previously (Power and Elliott, 2006). The present study used data of the exposures, mediators, and covariates from the 44 y and 46 y waves; the 50 y, and 55 y waves were used to estimate incident cases of depression.

2.2. Depression

To reduce the possibility of reverse causality, we considered as prevalent cases of depression those reporting a diagnosis of depression until the 46 y wave or at risk for common mental disorders (based on the Clinical Interview Schedule-Revised-CIS-R) at the 44 y wave (Lewis et al., 1992). The CIS-R instrument is a valid screening instrument for common mental disorders. Given the co-occurrence of different common mental disorders with depression, we opted to use the total score that indicates the risk for the presence of common mental disorders, adopting the cut-off point of $\geq$12 to consider those at risk for common mental disorders as prevalent cases. At the 46 y wave, psychiatric histories were assessed, asking about the previous diagnosis of depression and at which age the participants received the diagnosis. At wave 50 y, the participants were asked whether they visited a physician since the previous wave to treat depression and whether they still suffered from this condition. At the 55 y wave, the participants were asked if, since the previous wave, they suffered with depression. We considered as incident cases of depression those without depression until the 46 y wave, who started to report depression at the 50 y or 55 y waves.

2.3. Mentally-passive and mentally-active sedentary behavior (at 44 y)

Two categories of sedentary behavior were assessed using the validated EPIC-Norfolk Physical Activity Questionnaire (EPAQ2) (Wareham et al., 2002). Mentally-passive sedentary behavior was assessed with the question "How much time did you spend on average during the last year watching TV or videos, other than for work." Possible answers were: A) None, B) <1 h/d, C) 1 to 2 h/d, D) 3 or 4 h/d, or E) >4 h/day. Mentally-active sedentary behavior was assessed with items on activities during worktime, which included a checkbox (yes or no), and the duration in hours per week for different activities of sitting, standing, and walking. In this part of the questionnaire, participants were asked to report the time spent weekly in activities "Sitting — light work e.g. desk work, or driving a car or truck", which we considered as our indicator of mentally-active sedentary behavior. Similar to previous studies (Hallgren et al., 2018, 2020b), and considering that the cut-off point also corresponds to approximately the highest quintile for mentally-passive and highest tertile for mentally-active sedentary behaviors, we adopted the cut-off point of $\geq$3 h/d for both behaviors.

2.4. Mediators (at 44 y)

We examined waist circumference, C-reactive protein, and glycated hemoglobin assessed at the 44 y wave as potential mediators. Waist circumference was measured at the midpoint between the lower ribs and iliac crest (i.e., mid-axillary line) by using a tape. Participants were asked to wear loose fitting garments without a belt and to relax their abdominal muscles. C-reactive protein and glycated hemoglobin were measured through non-fasting blood samples, which were sent to collaborating laboratories. C-reactive protein was estimated using immunonephelometry (Dade Behring, Milton Keynes, United Kingdom). Glycated hemoglobin was estimated using the ion-exchange high-performance liquid chromatography technique (HLC-723GHbA1c 2.2; Tosoh Corp, Tokyo Japan). We used the mediators as continuous variables. Specifically for C-reactive protein, we excluded those with C-reactive protein higher than 10 mg/L, which likely indicate cases of acute inflammation due to infectious or inflammatory diseases.

2.5. Covariates (at 44y)

We adjusted our analyses for gender, education, employment status, physical activity, tobacco smoking, and alcohol consumption, based on previous studies on this topic (Hallgren et al., 2020c; Werneck et al., 2021). Education was estimated using the self-reported highest academic achievement and classified as primary school, high school, and tertiary education. Employment status was ascertained by asking the participants if they were in paid employment. Physical activity was assessed using a modified version of the EPAQ2 (Wareham et al., 2002), excluding the home activity questions. Considering that leisure-time physical activity is the domain most consistently associated with depression, we only included this domain in our analysis. Tobacco smoking was assessed by asking about current smoking status. Alcohol

consumption was assessed by asking about the frequency and quantity of alcohol consumed. We considered habitual alcohol consumers to be those drinking four or more times a week.

2.6. Statistical analyses

The characteristics of the sample are presented using values of absolute and relative frequencies or mean and standard deviation. Chi-square and Mann-Whitney tests were used to compare the groups with and without incident depression. We used Poisson regression first to investigate the cross-sectional association between mentally-passive and mentally-active sedentary behaviors, adjusting for gender, education, employment status, physical activity, tobacco smoking, and alcohol consumption. The associations of mentally-passive and mentally-active sedentary behaviors with incident depression were then analyzed using Cox proportional hazards regression models, reporting hazard ratios (HR) and their respective 95 % confidence interval (CI). Participants were assessed at the midpoint between the last wave free of depression and the first wave with the report of depression or at the last wave with a valid date, whichever came first. We tested the proportional hazards assumption, and the variables not attending the assumption were included as strata in the models. We created four gender-adjusted and fully-adjusted models: Model A (i.e., the base model): The independent associations of mentally-passive and mentally-active sedentary behavior with incident depression; Model B: the base model plus waist circumference; Model C: the base model plus C-reactive protein; Model D: base model plus glycated hemoglobin.

The role of waist circumference, C-reactive protein, and glycated hemoglobin in the association between mentally-passive sedentary behavior and incident depression was investigated through mediation models (Fig. 1).

We adopted the counterfactual approach (Valeri and Vander Weele, 2013). The counterfactual approach has the advantage of dealing with potential interactions between the exposure and the mediators, which is crucial for our models considering that mentally-passive sedentary behavior and the mediators were assessed during the same wave. In the counterfactual approach, total effect (i.e., the effect of mentally-passive sedentary behavior on incident depression) is decomposed into controlled direct effects (i.e., the effect of mentally-passive sedentary behavior on incident depression not explained by the mediators) and pure indirect effects (i.e., the mediation effect). Furthermore, the counterfactual approach also permits the estimation of the causal association derived from the interaction between the exposure and mediators, such as estimating the reference interaction (i.e., the effect of mentally-passive sedentary behavior on incident depression due to the interaction with the mediators) and mediated interaction (i.e., the effect of the interaction of mentally-passive sedentary behavior with mediators that is activated when mentally-passive sedentary behavior has an effect on the mediators capturing both the interaction and mediation effect) (Discacciati et al., 2019). Considering the assumptions of causal mediation analysis, we included all the covariates in the models (i.e., gender, education, employment status, physical activity, tobacco smoking, and alcohol consumption). More details of the DAG model can be found in the DAGitty: http://dagitty.net/dags.html?id=eLgnf. We created one mediation model for each potential mediator. All analyses were conducted in Stata 15.1.

3. Results

The characteristics of the sample are presented in Table 1. There were 636 cases of incident depression over 47,184 person-years. The prevalence of ≥3 h/d of mentally-passive sedentary behavior was 19.8 % in the whole sample and higher among the participants with incident cases of depression (27.5 % vs. 18.6 %). Participants with incident depression also had a lower prevalence of ≥3 h/d mentally-active sedentary behavior (32.7 % vs. 40.9 %). In the attrition analysis comparing the included and the excluded samples, the included sample had a slightly higher proportion of women (51.8 % vs. 48.7 %), as well as higher education (more than high school: 28.2 % vs. 25.2 %). More time in mentally-active sedentary behavior was inversely associated with higher mentally-passive sedentary behavior (prevalence ratio: 0.82; 95%CI: 0.72; 0.92).

Table 2 and Fig. 2 show the associations of mentally-passive and mentally-active sedentary behaviors with incident depression. In the fully adjusted models, mentally-passive sedentary behavior was associated with a higher hazard for depression (HR: 1.43; 95%CI: 1.19–1.71), but that was not the case for mentally-active sedentary behavior (HR: 0.92; 95%CI: 0.77–1.10).

Although all the three potential biological mediators (waist circumference, C-reactive protein, and glycated hemoglobin) were associated with incident depression in the models, only the inclusion of waist circumference and C-reactive protein reduced the association between mentally-passive sedentary behavior and incident depression (HR: 1.36; 95%CI: 1.13–1.64 and HR: 1.38; 95%CI: 1.15–1.66, respectively).

The mediation models for waist circumference, C-reactive protein, and glycated hemoglobin are presented in Table 3 and are also shown in Fig. 2. Waist circumference (coefficient: −0.03; 95%CI: −0.05; −0.01; 9.2 %) and C-reactive protein (coefficient: −0.03; 95%CI: −0.04; −0.01; 8.3 %) partly mediated the association between mentally-passive sedentary behavior and incident depression, while glycated hemoglobin did not influence the association.

4. Discussion

We investigated the associations of mentally-passive and mentally-active sedentary behavior with incident depression, and the role of potential biological mediators. Our main findings were that higher volumes of time spent in mentally-passive sedentary behavior were associated with higher hazards for incident depression, while there was no association for mentally-active sedentary behavior. C-reactive protein and waist circumference partly mediated the association between mentally-passive sedentary behavior and incident depression, but glycated hemoglobin did not do so.

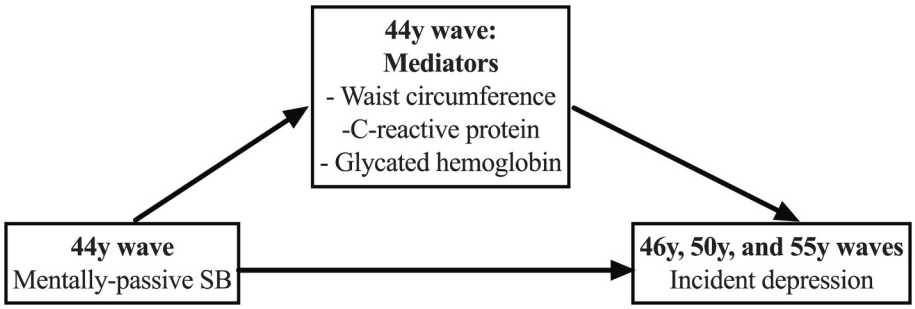

Fig. 1. Theoretical mediation model.

Table 1
Characteristics of the sample.

Variable	Categories/unit	Whole sample	Incident depression		*p*
		(n = 4607)	No (n = 3971)	Yes (n = 636)	
Gender	Men	2287 (49.6)	2067 (52.1)	220 (34.6)	<0.001
	Women	2320 (50.4)	1904 (48.0)	416 (65.4)	
Country	England	3939 (85.5)	3402 (85.7)	537 (84.4)	0.560
	Wales	210 (4.6)	176 (4.4)	34 (5.4)	
	Scotland	458 (9.9)	393 (9.9)	65 (10.2)	
Education	Low	577 (12.5)	473 (11.9)	104 (16.4)	0.007
	Medium	2708 (58.8)	2348 (59.1)	360 (56.6)	
	High	1322 (28.7)	1150 (29.0)	172 (27.0)	
Mentally-active SB	<3 h/d	2775 (60.2)	2347 (59.1)	428 (67.3)	<0.001
	≥3 h/d	1832 (39.8)	1624 (40.9)	208 (32.7)	
Mentally-passive SB	<3 h/d	3694 (80.2)	3233 (81.4)	461 (72.5)	<0.001
	≥3 h/d	913 (19.8)	738 (18.6)	175 (27.5)	
Waist circumference	cm	91.0 (13.1)	91.0 (13.0)	90.9 (14.1)	0.280
C-reactive protein	mg/L	1.6 (1.8)	1.5 (1.7)	1.9 (2.2)	<0.001
Glycated hemoglobin	%	5.2 (0.6)	5.2 (0.6)	5.3 (0.7)	0.923
Alcohol	<4 times/week	3366 (73.1)	2876 (72.4)	490 (77.0)	0.015
	≥4 times/week	1241 (26.9)	1095 (27.6)	146 (23.0)	
Tobacco	No	3521 (76.4)	3055 (76.9)	466 (73.3)	0.043
	Yes	1086 (23.6)	916 (23.1)	170 (26.7)	
Exercise	Minutes	92.4 (189.9)	92.0 (185.6)	95.2 (215.1)	0.291
Employment status	No	337 (7.3)	246 (6.2)	91 (14.3)	<0.001
	Yes	4270 (92.7)	3725 (93.8)	545 (85.7)	
Depressive symptoms	score	0.2 (0.5)	0.1 (0.5)	0.3 (0.6)	<0.001

Note. Values presented as absolute and relative frequencies or mean and standard deviation. *p*-Values are derived from the chi-square test (i.e., for categorical variables) or Mann-Whitney test (i.e., for continuous variables).

Our null findings regarding the association between mentally-active sedentary behavior and incident depression are partly in line with previous studies. Although most studies investigating these relationships found no associations (Huang et al., 2020; Werneck et al., 2021), others found an inverse association (Hallgren et al., 2018, 2020b). Interestingly, both studies from the Swedish National March Cohort also considered a similar indicator of occupational sitting time as mentally-active sedentary behavior (Hallgren et al., 2018, 2020b), but differences in the question may partly explain the divergent findings. In the present study, other options regarding types of activity during worktime were also presented (e.g., sitting — moderate work, standing — light work, standing — moderate work, walking at work, moving and pushing heavy objects), while the Swedish cohort presented one question about office work, sitting in a meeting, knitting/sewing (Hallgren et al., 2018, 2020b). Therefore, it is possible that disaggregating more categories of activity during worktime captures a 'purer' sedentary behavior, without light physical activity. In addition, our indicator also captures other behaviors such as driving a vehicle, which is a mentally-active sedentary behavior, but a previous study found an association with depression (Sui et al., 2015). It is also worth mentioning that the sample size of our study was considerable lower than the previous studies from the Swedish cohort, which included >20,000 participants (Hallgren et al., 2018, 2020b).

Table 2
Associations of mentally-passive and mentally-active sedentary behavior with incident depression and the role of the potential mediators (n = 4607).

	Gender-adjusted	Fully adjusted
	HR (95%CI)	HR (95%CI)
Model A (base model)		
MA SB (ref ≤3 h/d)	0.84 (0.72–0.99)	0.92 (0.77–1.10)
MP SB (ref ≤3 h/d)	1.56 (1.31–1.86)	1.43 (1.19–1.71)
Model B		
MA SB (ref ≤3 h/d)	0.85 (0.72–1.01)	0.93 (0.77–1.11)
MP SB (ref ≤3 h/d)	1.47 (1.23–1.76)	1.36 (1.13–1.64)
Waist circumference, cm	1.01 (1.01–1.02)	1.01 (1.01–1.02)
Model C		
MA SB (ref ≤3 h/d)	0.83 (0.70–0.98)	0.91 (0.76–1.09)
MP SB (ref ≤3 h/d)	1.50 (1.26–1.79)	1.38 (1.15–1.66)
C-reactive protein, mg/L	1.08 (1.04–1.12)	1.07 (1.03–1.11)
Model D		
MA SB (ref ≤3 h/d)	0.85 (0.72–1.01)	0.93 (0.78–1.12)
MP SB (ref ≤3 h/d)	1.53 (1.29–1.83)	1.42 (1.18–1.70)
Glycated hemoglobin	1.16 (1.03–1.29)	1.15 (1.03–1.29)

Note. Model A: models for the independent associations of mentally-passive and mentally-active sedentary behavior with incident depression. Model B: Model A plus waist circumference. Model C: Model A plus C-reactive protein. Model D: Model A plus glycated hemoglobin. Fully adjusted models were adjusted for gender, education, employment status, physical activity, tobacco smoking, and alcohol consumption.

Our finding of an association between mentally-passive sedentary behavior and depression is consistent with previous longitudinal studies which have adopted similar exposures (Hallgren et al., 2018; Huang et al., 2020; Werneck et al., 2021). Given the bidirectional nature of these relationships, our large prospective study adds important new evidence on these associations. Our findings are also in line with a recent proposal of including cognitive engagement in a sedentary behavior taxonomy (Taylor, 2022). We note that based in our findings and those of previous studies related to mentally-passive and mentally-active sedentary behaviors (Hallgren et al., 2018; Huang et al., 2020; Werneck et al., 2021), the cognitive domain of the taxonomy seems to be more relevant to mental health-related outcomes than the social interaction, novelty and choice domains.

In addition to identifying relationships between mentally-passive sedentary behaviors and incident depression, we also investigated the role of possible mediators of this association. Inflammation is a recognized possible mechanism linking sedentary behavior and depression (Hallgren et al., 2016). Moreover, there is evidence linking sedentary behavior and inflammation as well as evidence linking inflammation and depression (Howard et al., 2015). Our finding that C-reactive protein partly mediated (i.e., 8.3 %) the association between mentally-passive sedentary behavior and depression supports this hypothesis. A previous clinical trial found that participants with greater mood disturbance following an intervention with induced sedentary behavior also presented with elevated levels of the pro-inflammatory marker IL-6, indicating the possible role of inflammation linking mentally-passive sedentary behavior and depression (Endrighi et al., 2016). Higher durations of sedentary behavior, especially in mentally-passive activities,

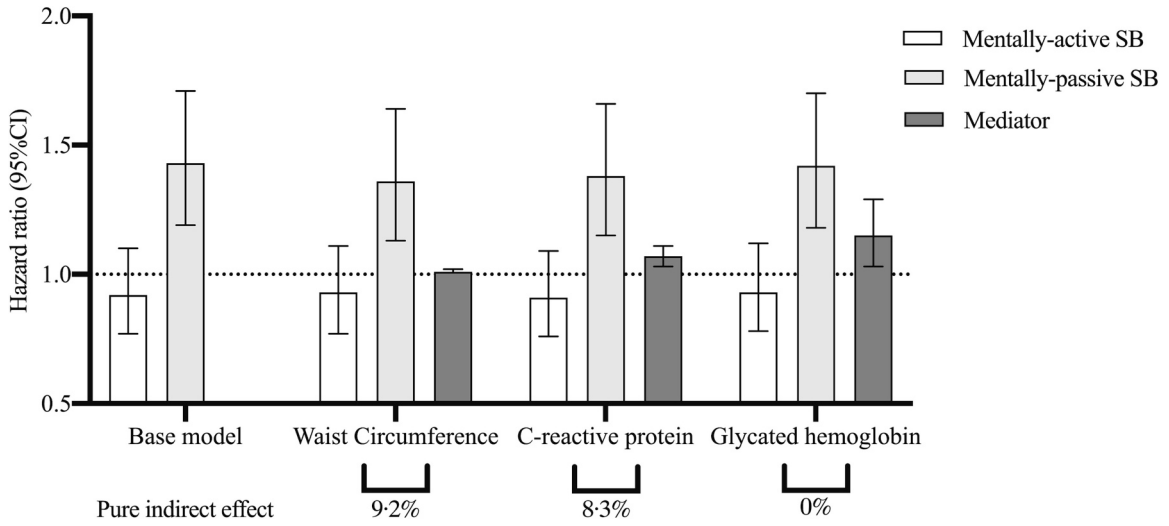

Fig. 2. Associations of mentally-passive and mentally-active sedentary behavior as well as mediational relationships for waist circumference, C-reactive protein, and glycated hemoglobin with incident depression (fully-adjusted hazard ratios). Note. SB, sedentary behavior. Adjusted for gender, education, employment status, physical activity, tobacco smoking, and alcohol consumption. The pure indirect effects refer to the influence of the mediators in the association between mentally-passive sedentary behavior and incident depression.

Table 3
Mediation models of waist circumference, C-reactive protein and glycated hemoglobin in the association between mentally-passive sedentary behavior and incident depression (n = 4607).

	Waist circumference	C-reactive protein	Glycated hemoglobin
	Coefficient (95%CI)	Coefficient (95%CI)	Coefficient (95%CI)
Gender-adjusted			
Total effect	−0.34 (−0.46; −0.22)	−0.36 (−0.48; −0.25)	−0.37 (−0.48; −0.25)
Controlled direct effect	−0.31 (−0.44; −0.19)	−0.00 (−0.01; 0.01)	0.01 (−0.05; 0.06)
Reference interaction	0.03 (−0.01; 0.06)	−0.34 (−0.47; −0.21)	−0.36 (−0.50; −0.23)
Mediated interaction	−0.03 (−0.06; 0.01)	0.01 (−0.02; 0.04)	0.01 (−0.01; 0.02)
Pure indirect effect	−0.03 (−0.06; −0.01)	−0.03 (−0.06; −0.01)	−0.01 (−0.02; −0.01)
Proportion of pure indirect effect	9.6 %	9.6 %	3.0 %
Fully-adjusted			
Total effect	−0.27 (−0.41; −0.13)	−0.31 (−0.44; −0.17)	−0.31 (−0.44; −0.18)
Controlled direct effect	−0.25 (−0.39; −0.11)	−0.28 (−0.42; −0.15)	−0.30 (−0.43; −0.18)
Reference interaction	0.03 (−0.01; 0.06)	0.00 (−0.02; 0.02)	0.00 (−0.01; 0.01)
Mediated interaction	−0.02 (−0.05; 0.01)	0.01 (−0.02; 0.03)	0.00 (−0.01; 0.01)
Pure indirect effect	−0.03 (−0.05; −0.01)	−0.03 (−0.04; −0.01)	−0.01 (−0.01; 0.00)
Proportion of pure indirect effect	9.2 %	8.3 %	–

Note. Fully adjusted models were adjusted for gender, education, employment status, physical activity, tobacco smoking, and alcohol consumption. The coefficients represent excess hazard ratio.

are associated with longer periods of uninterrupted sedentary behavior (Shibata et al., 2019). Considering that muscle contractions are associated with the production of pro-inflammatory cytokines, exposure to long periods of time without muscle contractions may be associated with the elevation of low-grade inflammation (Hamilton et al., 2008).

Similarly, waist circumference partly mediated the association between mentally-passive sedentary behavior and depression (i.e., 9.2 %). The association between sedentary behavior with adiposity is well known, as sedentary behavior requires minimal energy expenditure and mentally-passive sedentary behaviors frequently displace time in physical activity (Hallgren et al., 2020b). In addition, obesity is associated with depression through different mechanisms (Luppino et al., 2010). Another possibility is that waist circumference could be a proxy for the overall health situation of the participant, and in that case, waist circumference is frequently correlated with other chronic diseases (Ross et al., 2020). Therefore, it is possible that part of the association between waist circumference and depression derives from the development of other chronic diseases.

In addition to their independent role, it is also possible that the association between mentally-passive sedentary behavior and incident depression can be through an interrelationship between inflammation and adiposity (Capuron et al., 2017). In this sense, a higher exposure to mentally-passive sedentary behavior would be associated with higher adiposity, which in turn would be associated with increased inflammation, and consequently would lead to an increased hazard for developing depression.

Although not the focus of the current study, we acknowledge that psychosocial mediators could also play a role in these relationships. Mentally-passive sedentary behaviors could reduce time spent in supportive social relationships, which might otherwise buffer stressful events and help to cope with rumination and reduce depressive symptoms (Hallgren et al., 2017). We also speculate that mentally-passive sedentary time could be associated with higher consumption of alcohol or ultra-processed/sweetened foods that may affect psychological wellbeing (Lane et al., 2022).

In contrast to findings on the other possible mediators, we did not find a mediation effect of glycated hemoglobin. Although glycated hemoglobin was associated with incident depression it was not associated with mentally-passive sedentary behavior, which is surprising, as most of the previous studies found an association between mentally-passive

sedentary behaviors such as TV viewing and incident diabetes. However, we note that other large studies also found null findings regarding the association between TV viewing and biomarkers related to glycemic control (Dempsey et al., 2018). Thus, future studies should clarify the role of glycated hemoglobin as a mediator between mentally-passive sedentary behaviors and incident depression.

Our study has several unique strengths, including the assessment of both mentally-passive and mentally-active sedentary behaviors, a long follow-up period allowing the emergence of a sufficient number of depression cases to power the analyses, and the assessment of possible biological mediators, advancing the exploration of possible mechanisms linking mentally-passive sedentary behaviors and depression. Also, to increase the prospective prediction, and reduced the potential impact of reverse causality, we prolonged our baseline period and considered cases at the 44y wave as prevalent cases of depression. We also considered the cases of risk for common mental disorders, measured by the CIS-R questionnaire as prevalent cases to avoid the underestimation of depression. Some potential limitations are also acknowledged. First, our exposures were self-reported, which may lead to possible bias including the underestimation of sedentary behavior (Kastelic and Šarabon, 2019). Second, the incidence of depression was based on self-reported diagnosis, which contains recall bias and may underestimate the cases of depression. However, a previous cohort study found an elevated agreement between self-reported diagnosis and assessed depression (Sanchez-Villegas et al., 2008). Third, the range of sedentary behaviors assessed was limited and did not include screen-based sitting, which has become highly prevalent and linked to depression (Huang et al., 2020). Fourth, although we considered total time sitting while doing light activities during worktime as mentally-active sedentary behavior, it is plausible that some of this time was mentally-passive (e.g., sitting while waiting, or sitting while doing light mechanical activities), which may partly explain the lack of association between mentally-active sedentary behavior and incident depression in the current study. Fifth, it is also possible that with several technological advances since the baseline of this study (i.e., 2002), the patterns of sedentary behavior during workplace and leisure may have changed. Sixth, the exposures and mediators were assessed at the same wave, which limits the causality inference. However, the mediation method we used accounts for potential interactions between the exposure and mediator, reducing the bias. Seventh, the diagnosis of depression was self-reported, and it is possible that the cases represent more severe cases of depression. We note however, that the United Kingdom's health system (the National Health Service) is a public health system and residents can readily access physicians. Finally, there were only two follow-up waves and the date of depression diagnosis was not asked, which might bias our time-proportional models.

In conclusion, we found that mentally-passive and mentally-active sedentary behaviors had distinct associations with incident depression, with only significant associations only for mentally-passive sedentary behavior. Moreover, waist circumference and C-reactive protein partly mediated these relationships, shedding light on possible underlying mechanisms. While physical activity guidelines recommend reducing and breaking up sedentary time, our findings suggest that recommendations specific to mental health could emphasize reducing mentally-passive sedentary time. Our mediation findings also suggest that those at risk for depression and with high levels of mentally-passive sedentary behaviors could benefit from assistance to reduce waist circumference and C-reactive protein via increased levels of physical activity. In addition, our findings suggest the potential importance of jointly addressing metabolic and mental health in future research, and in public health and clinical practice. Future studies should investigate the association with incident depression of objectively measured screen-use behaviors that are likely to be more mentally-passive (television and video viewing) or more mentally-active (video gaming), as well as the role of other potential mediators such as those related to neuroplasticity.

CRediT authorship contribution statement

AOW: Conceptualization; Formal analysis; Writing – original draft. NO: Visualization; Writing – review & editing; Supervision. RHOA and DRS: Writing – review & editing; Validation. MH: Writing – review & editing; Supervision. AOW and RHOA had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

Ethical standards

All the procedures were approved by the South East Multicentre Research Ethics Committee for the 44y wave (01/1/44), by an internal ethics committee for the 46y wave, by the London Multicentre Research Ethics Committee for the 50y (08/H0718/29) waves, and by the London – Central (12/LO/2010) for the 55y wave. The procedures were carried out in accordance with the Helsinki Declaration of 1975, as revised in 2008. Participants provided informed consent.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data from the 1958 National Child Development Study are available in the UK Data Service repository (https://www.ukdataservice.ac.uk).

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