

Research report

Lifestyle-related risk factors and their cumulative associations with hippocampal and total grey matter volume across the adult lifespan: A pooled analysis in the European Lifebrain consortium

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ABSTRACT

Background: Lifestyle-related risk factors, such as obesity, physical inactivity, short sleep, smoking and alcohol use, have been associated with low hippocampal and total grey matter volumes (GMV). However, these risk factors have mostly been assessed as separate factors, leaving it unknown if variance explained by these factors is overlapping or additive. We investigated associations of five lifestyle-related factors separately and cumulatively with hippocampal and total GMV, pooled across eight European cohorts.

Methods: We included 3838 participants aged 18–90 years from eight cohorts of the European Lifebrain consortium. Using individual person data, we performed cross-sectional meta-analyses on associations of presence of lifestyle-related risk factors separately (overweight/obesity, physical inactivity, short sleep, smoking, high alcohol use) as well as a cumulative unhealthy lifestyle score (counting the number of present lifestyle-related risk factors) with FreeSurfer-derived hippocampal volume and total GMV. Lifestyle-related risk factors were defined according to public health guidelines.

Results: High alcohol use was associated with lower hippocampal volume ($r = -0.10$, $p = 0.021$), and overweight/obesity with lower total GMV ($r = -0.09$, $p = 0.001$). Other lifestyle-related risk factors were not significantly associated with hippocampal volume or GMV. The cumulative unhealthy lifestyle score was negatively associated with total GMV ($r = -0.08$, $p = 0.001$), but not hippocampal volume ($r = -0.01$, $p = 0.625$).

Conclusions: This large pooled study confirmed the negative association of some lifestyle-related risk factors with hippocampal volume and GMV, although with small effect sizes. Lifestyle factors should not be seen in isolation

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as there is evidence that having multiple unhealthy lifestyle factors is associated with a linear reduction in overall brain volume.

1. Introduction

During healthy ageing volumes of grey matter brain structures are known to decrease overall, especially hippocampal and total grey matter volume (GMV) (Pomponio et al., 2020; Fjell et al., 2009; Walhovd et al., 2011). While total grey matter volume shows a slow but steady reduction in late adulthood, locally, brain volume can decrease more rapidly, with for example hippocampal volume displaying accelerated reduction after 50 years of age (Pomponio et al., 2020). This process of neurodegeneration may be negatively affected by modifiable factors such as lifestyle-related risk factors (Fotuhi et al., 2012; Batouli and Saba, 2017; Raz and Rodrigue, 2006; Taki et al., 2011). Lifestyle therefore could be an important target for intervention to prevent or slow atrophy and related cognitive decline (Fjell and Walhovd, 2010; Livingston et al., 2020). Unhealthy lifestyle has been related to processes with possible negative effects, such as inflammation, poorer cardio-metabolic health, and increased activity of the hypothalamic–pituitary–adrenal (HPA) axis (Mandelli et al., 2022), and also to chronic diseases such as cardiovascular disease (Li et al., 2020), diabetes (Schlesinger et al., 2020), and hypertension (Nguyen et al., 2019). These disturbed processes have also been related to decreases of brain structures (Fotuhi et al., 2012; Frisoni et al., 2010). Especially the hippocampus seems to be sensitive to negative effects of for example stress via extended exposure to glucocorticoids (Sapolsky, 2000), and neuroinflammation (Barrientos et al., 2015).

Lifestyle-related risk factors, such as overweight or obesity, physical inactivity, short sleep, smoking and high alcohol use, have been associated with lower total GMV (Daviet et al., 2022; Gray et al., 2020; Wittfeld et al., 2020; Fernández-Andújar et al., 2021; Kim et al., 2022), and in particular lower hippocampal volume (Topiwala et al., 2017; Logtenberg et al., 2022; Erickson et al., 2014; Dekkers et al., 2019; Scullin, 2017). These lifestyle-related risk factors are also known to co-occur within individuals (Noble et al., 2015). To explore whether effects of different types of unhealthy lifestyle behaviours might be additive, with the risk of adverse health outcomes increasing with more unhealthy lifestyles, cumulative measures have been used to indicate the number of unhealthy lifestyle factors present in a person. Cumulative lifestyle measures have been related to (increased risk for) adverse health outcomes, such as hyperactivity of the HPA-axis and inflammation (Mandelli et al., 2022), cardiovascular disease (Dimovski et al., 2019; Foster et al., 2018), and even increased mortality (Ding et al., 2015; Loeff and Walach, 2012). This suggests that with more types of unhealthy lifestyle behaviours, the negative impact on somatic health increases. However, in relation to brain structures, lifestyle factors have mostly been studied in isolation. While it has been suggested that lifestyle-related risk factors have an additive effect on dementia (Livingston et al., 2020) and cumulative unhealthy lifestyle scores can predict cognitive decline (Schiepers et al., 2018) and higher brain age (Anatürk et al., 2021), little is known about the combined effects of lifestyle factors on regional or global brain structure.

Therefore, we tested if the lifestyle-related risk factors overweight or obesity, physical inactivity, short sleep, smoking, and high alcohol use, were associated with hippocampal volume and total GMV, pooled across eight European cohorts. We used public health guidelines to define healthy and unhealthy categories for each lifestyle factor. We also calculated a cumulative unhealthy lifestyle score, with 1 point for each unhealthy lifestyle factor, and examined associations of this cumulative score with hippocampal volume and total GMV. We expected the separate lifestyle factors, as well as the cumulative unhealthy lifestyle score, to be negatively related to volume of hippocampus and total grey matter. Using age and sex strata, we also explored if effects were similar across age-groups and sexes.

2. Material and methods

2.1. Population

A total of 3838 adult participants (18 years or older) were included from eight cohorts being part of the European Lifebrain consortium (Walhovd et al., 2018) (<http://www.lifebrain.uio.no/>) with available data on one or more lifestyle factors and MRI measures of the brain. The included cohorts were: the Berlin Study of Aging-II (BASE-II, Germany) (Bertram et al., 2014), Betula project (Sweden) (Nilsson et al., 1997), Cambridge Centre for Ageing and Neuroscience study (Cam-CAN, UK) (Shafto et al., 2014), Center for Lifebrain Changes in Brain and Cognition longitudinal studies (LCBC, Norway) (Walhovd et al., 2016; Fjell et al., 2018), Live Active Successful ageing study (LISA, Denmark) (Eriksen et al., 2016), Whitehall-II Imaging Sub-study (UK) (Filippini et al., 2014), Netherlands Study of Depression and Anxiety (NESDA, Netherlands) (Penninx et al., 2008), and Mood Treatment with Antidepressants or Running study (MOTAR, Netherlands) (Lever-Van Milligen et al., 2019). Additional information for all cohorts and details on inclusion/exclusion criteria are presented in the [Supplemental information](#).

2.2. Measurements

2.2.1. Lifestyle-related risk factors

All measures (lifestyle and non-lifestyle) were included from the same measurement wave. Detailed information on lifestyle assessment per cohort and category harmonisation across cohorts can be found in the [Supplemental information](#). Definition of healthy and unhealthy categories for each lifestyle factor were based on public health guidelines, following previous examples (e.g. LIBRA score, Schiepers et al., 2018). Inclusion of continuous lifestyle measures was not possible as continuous variables were not available for all cohorts for all lifestyles and harmonisation of measures across cohorts was complicated. For variables with potential non-linear associations, additional analyses were performed using three levels, if sufficient data was available.

Height and weight were assessed on-site for all cohorts, and body mass index (BMI, weight in kilograms/height in meters²) was dichotomised into ‘normal weight’ (BMI < 25) versus ‘overweight or obese’ (BMI ≥ 25) (World Health Organization, 2023a). The number of underweight (BMI < 18) persons was too low (n = 59) to form a separate category and was combined with ‘normal weight’. Physical activity was measured in metabolic equivalent of task (MET) minutes per week for most cohorts, except for Betula and BASE-II, for which comparable cut-offs were chosen (see [Supplemental information](#)). Following the guidelines by the World Health Organization (Kyu et al., 2016), up to 600 MET minutes per week was scored as ‘inactive’ (unhealthy) and more than 600 MET minutes as ‘active’ (healthy). Sleep duration was categorised as ‘short sleep’ (≤ 6 h, unhealthy) and ‘normal sleep’ (> 6 h, healthy) (Watson et al., 2015), based on self-report measures. As information on long sleep (> 10 h) was not available for three cohorts and infrequent in the four cohorts for which this data was available (n = 34), this was grouped with ‘normal sleep’. Smoking was categorised as ‘current smoker’ (unhealthy) and ‘no current smoker’ (healthy) (World Health Organization, 2023b). Alcohol use was categorised as ‘no or moderate alcohol use’ (women: 0–7 drinks/week, men: 0–14 drinks/week) versus ‘high alcohol use’ (women: > 7 drinks/week, men: > 14 drinks/week) (Alcoholism NI on AA and Drinking levels defined Internet, 2023).

As dichotomising traits could lead to loss of information, we checked

whether grouping obese (BMI>30) and overweight (BMI \geq 25 and <30) together, moderately active (MET minutes/week \geq 600 and <3000) and very active (MET minutes/week >3000) together and no alcohol use and moderate alcohol use (women: 0–7 drinks/week, men: 0–14 drinks/week) together may have masked differences in hippocampal volume and total GMV. All of these analyses were corrected for the same covariates as in the main analyses.

2.2.2. Cumulative unhealthy lifestyle score

The cumulative unhealthy lifestyle score was calculated by adding the number of unhealthy lifestyle-related risk factors, following previous examples of cumulative lifestyle risk scores (e.g. LIBRA score, Schiepers et al., 2018). For all persons with available data on at least four of the five lifestyle factors, the number of lifestyle-related risk factors was calculated, ranging from 0 ('No lifestyle-related risk factors') to a maximum of five ('Five lifestyle-related risk factors'). In case data for one of the lifestyle factors was missing, data was mean imputed and rounded based on the other four lifestyle factors.

2.2.3. Imaging acquisition and analysis

Hippocampal volume, total grey matter volume (GMV), and estimated total intracranial volume (ICV) were derived from T1 structural MRI scans using FreeSurfer version 6.0 or 5.3. Total hippocampal volume was calculated as the average of left and right hippocampal volumes, as earlier research did not suggest hemisphere differences in relation to lifestyle factors (Topiwala et al., 2017; Logtenberg et al., 2022; Erickson et al., 2014; Dekkers et al., 2019; Scullin, 2017). More detailed information on scanner type, FreeSurfer version and MR acquisition parameters for each cohort can be found in the Supplemental information. Based on unadjusted brain structure data, hippocampal volume or total GMV more than four standard deviations from the mean of the respective cohort was excluded to remove outliers (N = 1).

2.3. Statistical analyses

All statistical analyses were conducted in R (version 3.6.0). To explore correlations between lifestyle-related risk factors and between these factors and the cumulative unhealthy lifestyle score, Spearman rank-order correlations were performed per cohort and then pooled using the R package metafor (Viechtbauer, 2010). For analyses of the separate lifestyle factors with hippocampal volume and total GMV, point biserial correlations were performed for each cohort, corrected for age, sex, years of education, scanner (where applicable), and ICV. For analyses on the cumulative unhealthy lifestyle score with hippocampal volume or total GMV, Spearman rank-order correlations were run for each cohort, correcting for the same covariates. Additional analyses were performed also correcting for depressive symptom severity to rule out depression severity driving the associations, as depression was related to hippocampal volume and total GMV in two of the included cohorts (Binnewies et al., 2022). Data on depression severity was available for all cohorts except LISA; more information on depression instruments per cohort can be found in the Supplement. P-values and 95 % confidence intervals (CI) were calculated using bootstrap procedures with 5000 iterations. Analyses were only performed in cohorts with at least 10 participants in each lifestyle factor category.

The correlation estimates and CI's from the per-cohort analyses were pooled using random-effects models. All statistical tests were performed two-sided and corrected for multiple testing using Bonferroni correction for two brain regions ($\alpha = 0.025$). To test whether associations varied between young-to-mid adulthood and old-age and between sexes, analyses were repeated with participants within cohorts stratified by age (18–59 years, 60 years and older) and stratified by sex (without correction for age or sex, respectively). Only cohorts with at least 10 participants per group were included in the stratified analyses, and pooled effect sizes were only calculated if at least three cohort were included in the stratified analyses. The pooled correlation coefficients

were compared across age- and sexes with a Fisher's z-test using the Cocor package (Diedenhofen and Musch, 2015).

3. Results

3.1. Sample description

Descriptive statistics of the cohorts included in the meta-analyses are presented in Table 1. Eight cohorts from seven European countries were included, with a total of 3838 participants, of which 1829 were women (49 %). A total of 2827 participants had enough data available for computation of the cumulative unhealthy lifestyle score (i.e., four or more lifestyle-related risk factors). The age range across all cohorts was 18–90 years (see Fig. S1 for age distributions). Across all cohorts, the most prevalent lifestyle-related risk factor was overweight/obesity (51.4 %), with a lower prevalence for physical inactivity (8.6 %), short sleep (14.9 %), current smoking (10.9 %) and high alcohol use (25.2 %).

Correlations between the dichotomised lifestyle factors were limited ($r = |0.01-0.05|$), while all dichotomised lifestyle factors were moderately-to-strongly associated with the cumulative unhealthy lifestyle score ($r = 0.37-0.75$; Table S1).

3.2. Associations between lifestyle factors and brain structure

High alcohol use was associated with lower hippocampal volume relative to no or moderate drinking ($r = -0.10$, 95 % CI = -0.18 to -0.01, $p = 0.021$), but none of the other lifestyle factors were associated with hippocampal volume (Fig. 1 and Table S2, $r = -0.09 - r = 0.04$, $p = 0.068 - p = 0.899$). Overweight/obesity was associated with lower total GMV compared to normal weight ($r = -0.09$, 95 % CI = -0.13 to -0.04, $p = 0.001$). Short sleep, high alcohol use and physical inactivity were not associated with total GMV (Fig. 1 and Table S2, $r = -0.04 - r = -0.04$, $p = 0.088 - p = 0.650$). Current smoking was associated with lower total GMV relative to no current smoking ($r = -0.09$, 95 % CI = -0.18 to -0.0003, $p = 0.049$), although this was not significant when correcting for multiple comparisons. Results remained similar when also correcting for depressive symptoms.

To check whether dichotomisation of lifestyle factors may have masked differences in hippocampal volume and total GMV, additional analyses were done with variables including three levels for BMI, physical activity and alcohol use. Associations with hippocampal volume or total GMV were not different between being overweight or obese, moderately active or very active, and between no or moderate alcohol use (Table S3).

3.3. Associations between cumulative unhealthy lifestyle score and brain structure

The cumulative unhealthy lifestyle score was significantly negatively associated with total GMV ($r = -0.08$, 95 % CI = -0.14 to -0.03, $p = 0.001$; Fig. 2 and Table S4) but not with hippocampal volume ($r = -0.01$, 95 % CI = -0.05–0.03, $p = 0.625$). Results remained similar when also correcting for depressive symptoms.

3.4. Effect of age and sex

The sample sizes per age-group and per sex for each of the lifestyle factors and the cumulative unhealthy lifestyle score are presented in Table S5. Associations between the cumulative unhealthy lifestyle score and hippocampal volume or total GMV were not different across age-groups or sexes (Fig. 3 and Table S6). Some associations between individual lifestyle factors and brain structures were different across age-groups, with correlation coefficients differing between the groups. However, differences between groups were rather inconsistent, with only few differences in associations between groups surviving correction for multiple corrections. Also, associations were not always in line with

Table 1
Demographic characteristics per cohort.

	Whitehall-II (n = 773)	LISA (n = 333)	LCBC (n = 816)	Cam-CAN (n = 641)	Betula (n = 341)	BASE-II (n = 423)	NESDA (n = 286)	MOTAR (n = 125)	Total (n = 3738)
	Oxford University, United Kingdom	Copenhagen University Hospital, Denmark	University of Oslo, Norway	Cambridge University, United Kingdom	Umea University, Sweden	Max Planck Institute, Germany	VU University, Netherlands	VU University, Netherlands	
Demographics									
Age, range	60–84	60–71	18–90	18–89	25–81	24–81	18–57	19–70	18–90
Age, mean years (SD)	69.8 (5.2)	66.5 (2.5)	39.0 (18.2)	54.9 (18.4)	62.2 (13.1)	62.2 (16.5)	37.6 (10.2)	38.6 (13.4)	55.2 (18.8)
Sex, female, n (%)	150 (19.4 %)	202 (60.7 %)	547 (67.0 %)	323 (50.4 %)	180 (52.8 %)	167 (39.5 %)	195 (50.5 %)	65 (52.0 %)	1829 (48.9 %)
Education, mean years (SD)	14.7 (3.3)	14.4 (2.0)	16.3 (2.7)	16.9 (3.8)	12.9 (4.2)	14.2 (2.8)	12.8 (3.2)	12.5 (3.5)	14.9 (3.5)
BMI									
Normal weight, n (%)	326 (42.2 %)	155 (46.5 %)	489 (61.3 %)	278 (49.9 %)	121 (35.8 %)	125 (36.3 %)	164 (57.3 %)	71 (56.8 %)	1729 (48.6 %)
Overweight/obese, n (%)	447 (57.8 %)	178 (53.5 %)	309 (38.7 %)	279 (50.1 %)	217 (64.2 %)	219 (63.7 %)	122 (42.7 %)	54 (43.2 %)	1825 (51.4 %)
Physical activity									
Active, n (%)	728 (94.2 %)	272 (84.5 %)	200 (94.8 %)	569 (99.3 %)	240 (70.4 %)	212 (74.6 %)	241 (88.6 %)	94 (76.4 %)	2556 (91.4 %)
Inactive, n (%)	45 (5.8 %)	50 (15.5 %)	11 (5.2 %)	4 (0.7 %)	101 (29.6 %)	72 (25.4 %)	31 (11.4 %)	29 (23.6 %)	242 (8.6 %)
Sleep duration									
Normal sleep, n (%)	690 (89.3 %)	–	541 (91.5 %)	564 (89.2 %)	272 (82.7 %)	312 (79.2 %)	197 (76.4 %)	91 (72.8 %)	2667 (86.0 %)
Short sleep, n (%)	83 (10.7 %)	–	50 (8.5 %)	68 (10.8 %)	57 (17.3 %)	82 (20.8 %)	61 (23.6 %)	34 (27.2 %)	435 (14.0 %)
Smoking									
No current smoker, n (%)	742 (96.7 %)	300 (90.1 %)	151 (84.8 %)	590 (92.3 %)	349 (92.3 %)	310 (86.8 %)	190 (66.4 %)	95 (77.9 %)	2727 (89.1 %)
Current smoker, n (%)	25 (3.3 %)	33 (9.9 %)	27 (15.2 %)	49 (7.7 %)	29 (7.7 %)	47 (13.2 %)	96 (33.6 %)	27 (22.1 %)	333 (10.9 %)
Alcohol use									
No/moderate alcohol use, n (%)	411 (53.8 %)	175 (53.8 %)	305 (90.8 %)	406 (83.9 %)	307 (94.5 %)	175 (84.1 %)	238 (83.5 %)	120 (97.6 %)	2137 (74.8 %)
High alcohol use, n (%)	353 (46.2 %)	157 (46.2 %)	31 (9.2 %)	78 (16.1 %)	18 (5.5 %)	33 (15.9 %)	47 (16.5 %)	3 (2.4 %)	720 (25.2 %)
Cumulative unhealthy lifestyle score									
Available, n (%)	773 (100 %)	321 (96.4 %)	289 (35 %)	415 (65 %)	338 (99 %)	286 (68 %)	282 (99 %)	123 (98 %)	2827 (73.7 %)
Median (IQR)	1 (1)	1 (1)	1 (1)	1 (1)	1 (0)	1 (1)	1 (1)	1 (2)	1 (1)
Brain									
Hippocampus volume, mean in cm ³ (SD)	3.7 (0.5)	3.9 (0.4)	4.2 (0.5)	4.0 (0.5)	3.9 (0.5)	3.9 (0.5)	4.0 (0.4)	4.0 (0.4)	3.9 (0.5)
Total GMV, mean in cm ³ (SD)	606.1 (50.8)	590.1 (47.6)	681.6 (74.1)	651.2 (70.8)	631.5 (61.3)	608.5 (61.1)	643.2 (59.5)	617.4 (66.4)	634.6 (70.1)
ICV, mean in cm ³ (SD)	1589.6 (205.9)	1448.5 (156.4)	1557.4 (169.8)	1573.1 (163.6)	1539.1 (158.6)	1305.2 (196.9)	1524.6 (173.9)	1331.3 (207.2)	1516.8 (202.2)

Note: Abbreviations: BMI=Body Mass Index, SD=standard deviation, IQR = interquartile range, GMV=grey matter volume, ICV=intracranial volume.

the expected direction of association. For example, in persons aged 60 years or older, smoking and overweight/obesity were associated with higher hippocampal volume relative to no smoking and normal weight, respectively, whereas there were no associations for smoking or overweight/obesity and hippocampal volume in persons younger than 60 years. Overweight/obesity was significantly associated with lower total GMV only in persons aged 60 years or older, but not in the younger age-group, whereas short sleep and high alcohol use were only related to lower total GMV in persons under 60 years, but not in the older age-group. Likewise, although some lifestyle-brain structure associations were different between men and women, these were not consistently stronger in any of the sexes. For example, high alcohol use was associated with lower hippocampal volume in women but not in men, while smoking was related to lower total GMV in men but not in women. Thus, no consistent differences between age-groups and sexes in associations between lifestyle and brain structures were observed.

4. Discussion

This pooled analysis of 3838 participants from eight European cohorts investigated associations between five lifestyle-related factors and a cumulative unhealthy lifestyle score with two structural brain volume measures: hippocampal volume and total grey matter volume (GMV). When investigating the lifestyle-related risk factors separately, high alcohol use was significantly associated with lower hippocampal volume, and overweight/obesity was associated with lower total GMV, although effect sizes were small. Short sleep, smoking and physical inactivity were not associated with hippocampal volume or total GMV. Furthermore, there was evidence of a cumulative effect of the lifestyle-related risk factors on brain health, as the cumulative unhealthy lifestyle score was associated with lower total GMV, suggesting that effects of lifestyle factors on brain structures might be additive. Associations were not consistently different across age-groups or sexes.

Based on previous studies, we hypothesised that overweight and

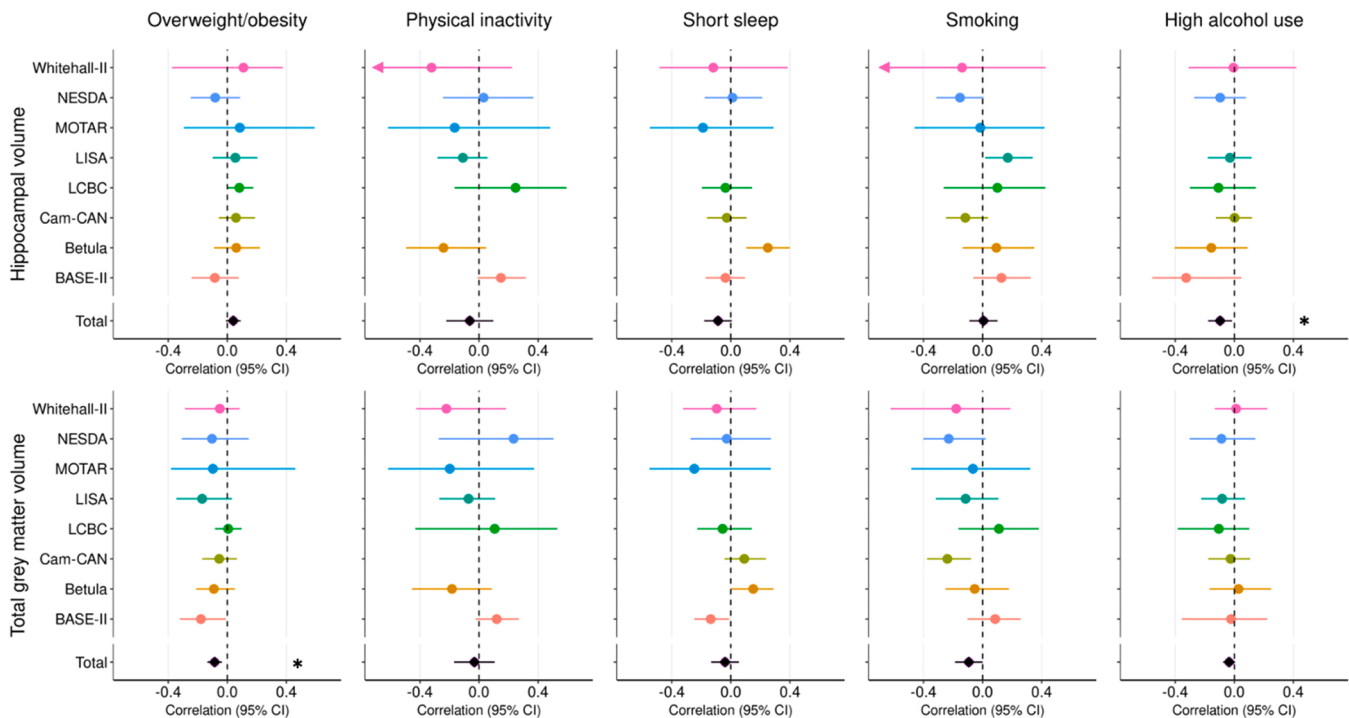


Fig. 1. Forest plots of associations of separate lifestyle factors with brain structure. Forest plots illustrating the associations of the separate lifestyle factors with hippocampal and total grey matter volume in the different cohorts (coloured circles), with random model pooled effect sizes (black diamonds), adjusted for age, sex, education, scanner, and intracranial volume. Horizontal lines represent 95 % confidence intervals (CI). Asterix indicates significance of pooled correlation: * $p < 0.05$ (corrected).

obesity, physical inactivity, short sleep, smoking and high alcohol use would be associated with smaller hippocampal and total GMV volumes. Several, but not all, of these associations were observed in the current study. Our findings suggest that high alcohol use was associated with lower hippocampal volume. This is in line with earlier studies describing increased alcohol consumption to be related to lower hippocampal volume (Topiwala et al., 2017; Wilson et al., 2017). Although previous studies have shown reduced GMV in relation to alcohol consumption (Daviet et al., 2022; Topiwala et al., 2022), this was not replicated in our current study. As Daviet et al. (2022) show in the sample of the UK Biobank, the magnitude of the effect increases with increasing alcohol intake and was present particularly in participants with very high levels of alcohol intake (>28 units/week), suggesting the threshold for high alcohol consumption used in the current study (>7/14 units/week) might be too low to detect reductions in total GMV. In our current analyses, overweight or obesity, compared to normal weight, was associated with lower total GMV. This is in line with other large studies observing lower total GMV with higher BMI and obesity (Hamer and Batty, 2019; Opel et al., 2020), and local reductions found throughout the whole brain in relation to an increased BMI and obesity (Fernández-Andújar et al., 2021; Opel et al., 2020; García-García et al., 2019). Overweight and obesity were not associated with hippocampal volume in our study, and previous studies have not been consistent with studies indicating no association (Hamer and Batty, 2019; García-García et al., 2019), a positive association (Opel et al., 2020), or a negative association (Dekkers et al., 2019), suggesting that overweight and obesity might have an effect on overall brain structure but not specifically on hippocampal volume. There was also a negative association between current smoking and total GMV, but this did not reach significance when correcting for multiple comparisons, and no association with hippocampal volume was observed. While some studies find associations between smoking and hippocampal volume (Logtenberg et al., 2022), others suggest that smoking is mainly related to global brain structure (Gray et al., 2020). We used current smoking as a measure of smoking

due to the limited information on former smokers across cohorts, even though it has been suggested that effects are stronger for lifetime smoking (Gray et al., 2020). Although short sleep has been associated with smaller brain volumes (Kim et al., 2022; Scullin, 2017), we did not find associations between short sleep and total GMV or hippocampal volume. This is in line with previous findings in part of the current sample, where sleep duration was not related to hippocampal volume (Fjell et al., 2019). However, in the current study we were not able to separate normal sleep from long sleep which could potentially mask effects. It has also been suggested that daytime tiredness and subjective sleep problems may be more related to brain structure than (objective) sleep duration (Fjell et al., 2022). We did not observe any associations between physical inactivity and total GMV or hippocampal volume, even though previous research found indications for these associations (Wittfeld et al., 2020; Erickson et al., 2014). However, prevalence of physical inactivity in the current sample was extremely low, limiting sensitivity to detect these associations. As self-reported physical activity may only moderately compare to more objective measures of physical activity, and may lead to under-reporting of physical activity (Difrancesco et al., 2019; Harris et al., 2009), future studies may benefit from using actigraphy or other objective measures of physical activity. As all lifestyle factors were dichotomised, additional analyses using variables with three categories were performed to check whether dichotomisation may have masked potential differences. Associations were not different between overweight or obesity, no and moderate alcohol, or being moderately or very active.

To explore whether effects of unhealthy lifestyle factors increase with a higher number of present factors, we investigated associations between a cumulative lifestyle score and hippocampal volume and total GMV. Despite the fact that not every lifestyle factor was significantly associated with GMV, the cumulative unhealthy lifestyle score was significantly negatively associated with total GMV. Thus, persons who had more lifestyle-related risk factors, had lower total GMV, which followed the pattern of a dose-response relationship. This is in line with

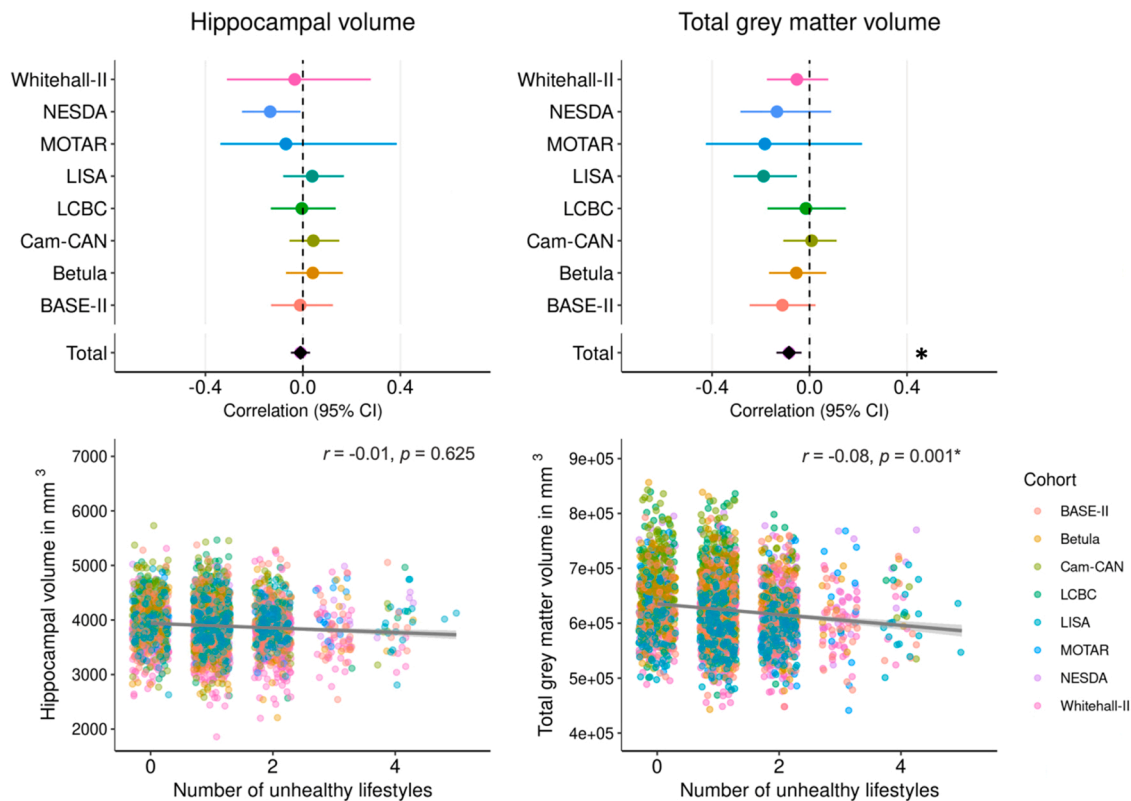


Fig. 2. Forest plots and scatterplots of associations of cumulative unhealthy lifestyle score with brain structures. The top panels show forest plots illustrating the associations of the cumulative unhealthy lifestyle score with hippocampal and total grey matter volume in the different cohorts (coloured circles), and the random model pooled effect sizes (black diamonds, with horizontal lines representing 95 % confidence intervals (CI), adjusted for age, sex, education, scanner, and intracranial volume. Bottom panels show scatterplots of the associations between cumulative unhealthy lifestyle score and hippocampal ($r = -0.01$, 95 % $CI = -0.05$ – 0.03 , $p = 0.625$) and total grey matter volume ($r = -0.08$, 95% $CI = -0.14$ to -0.03 , $p = 0.001$) across individuals (dots coloured by cohort), and fitted regression lines (dark grey line) with 95 % CI (light grey bands). Asterix indicates significance of pooled correlation: * $p < 0.05$ (corrected).

earlier reports showing that effects of an unhealthy lifestyle on somatic (Dimovski et al., 2019; Loeff and Walach, 2012) or mental health may add up (Adjibade et al., 2018; Velten et al., 2014). Unhealthy lifestyle is related to increased biological stress, such as overactivity of the HPA-axis and increased inflammation, and it has been suggested that there is an cumulative effect when multiple unhealthy lifestyle factors are present, with biological stress increasing with a higher number of lifestyle-related risk factors (Mandelli et al., 2022). Increased biological stress, in turn, may lead to neurodegeneration (Han and Ham, 2021; Green et al., 2021). However, the cumulative lifestyle score was not significantly related to hippocampal volume, suggesting that effects may not be uniform across the brain. This is in line with studies on some of the separate lifestyle factors showing more consistent associations with global brain structure (Gray et al., 2020; García-García et al., 2019). The effect of an unhealthy lifestyle on hippocampal volume may be more complex, with some lifestyle factors like overweight or obesity, sometimes being related to larger hippocampal volume (Opel et al., 2020), with overweight and moderate obesity in old age potentially associated with lower risk for dementia and neural atrophy (Bosello and Vanzo, 2021; Pegueroles et al., 2018).

Effects of age and sex on associations between lifestyle factors and brain structures were inconsistent. We could not find indications that effects of an unhealthy lifestyle are consistently stronger in older persons, as could be hypothesised because older persons have higher chances of more long-term exposure to lifestyle-related risk factors. On the other hand, somatic diseases, which are more prevalent with increasing age (Liberale et al., 2020), might lead to adoption of a healthier lifestyle, such as smoking cessation and reduced alcohol consumption ('sick-quitter hypothesis'; Wannamethee & Shaper, 1988) and the older age group may suffer from selective survival effects. Along

similar lines, weight-loss in old age might be an early indicator of dementia and other somatic diseases ('obesity paradox', Bosello & Vanzo, 2021; Singh-Manoux et al., 2018). However, although there were weak positive associations of hippocampal volume with overweight/obesity and smoking in elderly participants, fitting with the sick-quitter/obesity paradox, this notion was not consistently substantiated in our current study.

Some limitations of our study should be kept in mind. The use of categorical data for lifestyle-related risk factors may be a limitation, as continuous data might be more sensitive to the small effects often seen for associations of lifestyle factors and brain structures. Unfortunately, continuous data was not available for all variables in all cohorts, and they were difficult to harmonise across cohorts, limiting the options to perform analyses with finer-graded continuous variables. Although the dichotomous lifestyle measures were based on public health guidelines, in order to examine relations with the brain when adhering to general recommendations, cut-offs for low or high risk were not optimal for all variables, as the prevalence of some lifestyle-related risk factors was low. For example, across all cohorts, only 8.6 % of the participants reported being physically inactive (<600 MET minutes per week). This could be due to liberal guidelines for healthy lifestyle behaviour, measurement error or bias, as physical activity was based on self-report measures (Difrancesco et al., 2019; Harris et al., 2009; Miner et al., 2022).

Furthermore, as done in earlier research (Mandelli et al., 2022; Foster et al., 2018; Loeff and Walach, 2012; Schiepers et al., 2018), the cumulative unhealthy lifestyle score we used assumes all lifestyle-related risk factors contribute equally while some factors may be more harmful to brain structure than others (Livingston et al., 2020; Mackey et al., 2019). However, we show the associations of all

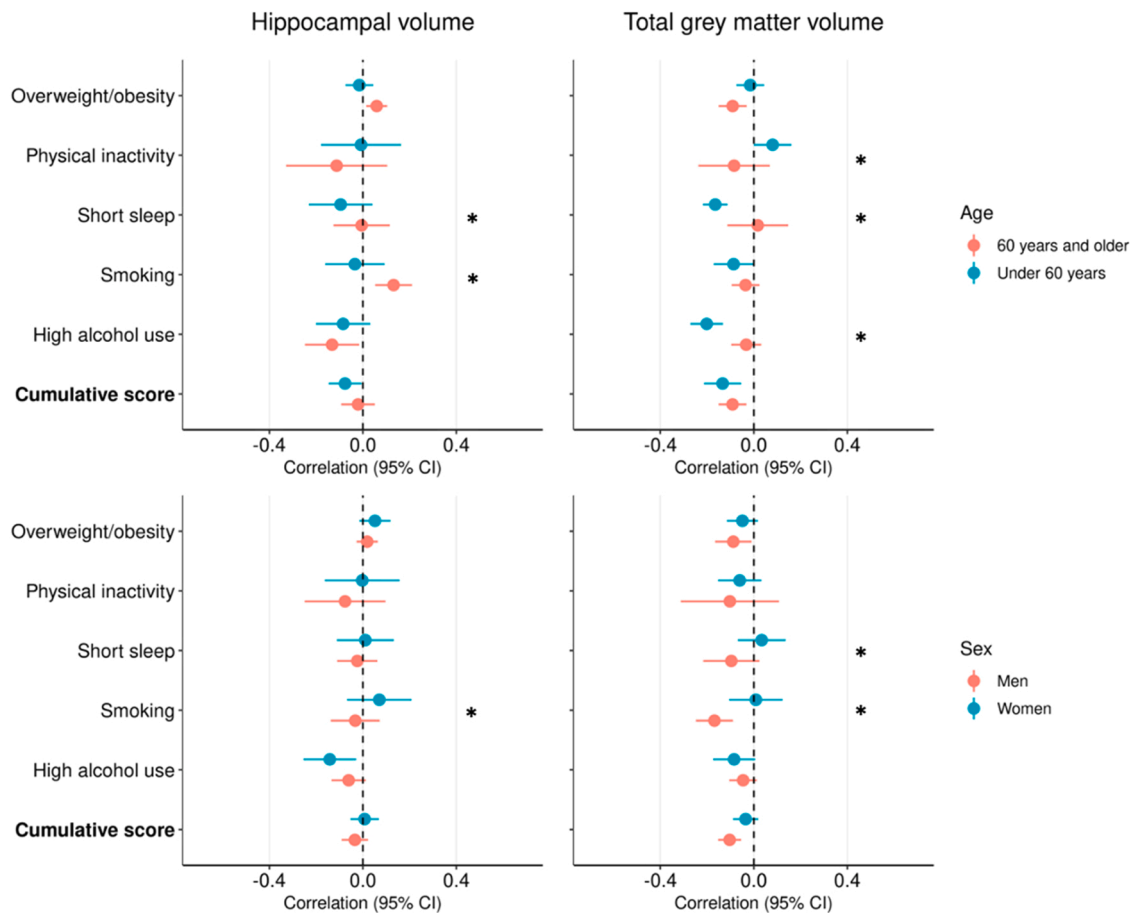


Fig. 3. Forest plots of pooled associations of separate lifestyle factors and cumulative unhealthy lifestyle score with brain structures per age-group and sex. Forest plots showing the random model pooled effect sizes of the associations of separate lifestyle factors and cumulative unhealthy lifestyle score with hippocampal and total grey matter volume per age-group and sex. Analyses within age-groups were adjusted for sex, education, scanner and intracranial volume, and analyses within sexes were adjusted for age, education, scanner and intracranial volume. Horizontal lines represent 95 % confidence intervals (CI). Asterisk indicates significance of comparisons of correlation coefficients between age-groups and between sexes: * $p < 0.05$ (corrected).

lifestyle-related risk factors with the included brain structures in separate analyses, and although not all lifestyle factors were significantly associated with the brain structures, we show that having multiple lifestyle-related risk factors is associated with a smaller GMV, suggesting additive effects. Future studies should investigate whether dose-dependent (cumulative) effects of lifestyle factors on brain structure are more clearly detectable when using continuous lifestyle data, and also explore cumulative lifestyle effects on other regional brain measures to explore if global effects might be driven by specific local effects. It is also important to note that the current analyses were based on cross-sectional data, and longitudinal studies are needed to discern potential causal effects as long-term exposure to an unhealthy lifestyle might be more detrimental (von Cederwald et al., 2022). Furthermore, the use of age groups to explore effects of age on associations of lifestyle factors and the included brain structures might be a limitation. While other approaches for analysing age effects, such as meta-regression or interaction analyses might be preferred, the substantial differences in mean age and age ranges across cohorts precluded us from using those approaches. Dividing the cohorts into two age groups allowed exploration of potential differences between young-to-middle aged participants and older participants. Although pooling our analyses across several large cohort studies increased the generalizability of our findings, this also might have led to increased noise and bias via methodological differences between studies, such as different FreeSurfer versions, scanner parameters, or lifestyle instruments.

Despite these limitations, strengths of the current study include the

large sample size by bringing together data from eight European cohorts, access to individual level data from all samples allowing for structured and consistent data analyses across cohorts and simultaneous inclusion of multiple lifestyles that allowed us to investigate their combined effects.

To conclude, the current pooled analysis of eight European studies confirmed negative associations between hippocampal and total grey matter volumes with some unhealthy lifestyle-related risk factors, such as high alcohol use and overweight or obesity. However, effect sizes were small and not consistently observed across brain measures and lifestyle factors. The cumulative unhealthy lifestyle score was related to lower total GMV, suggesting that having multiple unhealthy lifestyle factors is associated with a linear reduction in overall brain volume. Taken together, lifestyle factors should not only be studied in isolation but rather as a broader construct of an unhealthy lifestyle important for brain health. Therefore, lifestyle interventions aimed at improving brain health should be taking a broad perspective taking cumulative effects of lifestyle behaviours into account.

Declaration of Competing Interest

CAD is a cofounder, stock-owner, board member and consultant in the contract laboratory Vitas AS, performing personalised analyses of blood biomarkers. None of the other authors declare conflicts of interest.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.brainresbull.2023.110692](https://doi.org/10.1016/j.brainresbull.2023.110692).

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