International Journal of Obesity (2017), 1–7

www.nature.com/ijo

ORIGINAL ARTICLE

Body mass index is associated with cortical thinning with different patterns in mid- and late-life

ME Shaw[1], PS Sachdev[2], W Abhayaratna[3], KJ Anstey[3] and N Cherbuin[3]

OBJECTIVE: High BMI at midlife is associated with increased risk of dementia as well as faster decline in cognitive function. In late-life, however, high BMI has been found to be associated with both increased and decreased dementia risk. The objective of this study was to investigate the neural substrates of this age-related change in body mass index (BMI) risk.
METHODS: We measured longitudinal cortical thinning over the whole brain, based on magnetic resonance imaging scans for 910 individuals aged 44–66 years at baseline. Subjects were sampled from a large population study (PATH, Personality and Total Health through Life). After attrition and exclusions, the final analysis was based on 792 individuals, including 387 individuals aged 60–66 years and 405 individuals aged 44–49 years. A mixed-effects model was used to test the association between cortical thinning and baseline BMI, as well as percentage change in BMI.
RESULTS: Increasing BMI was associated with increased cortical thinning in posterior cingulate at midlife (0.014 mm kg^{-1} m^{-2}, confidence interval; CI = 0.005, 0.023, $P < 0.05$ false discovery rate (FDR) corrected). In late-life, increasing BMI was associated with reduced cortical thickness, most prominently in the right supramarginal cortex (0.010 mm kg^{-1} m^{-2}, CI = 0.005–0.016, $P < 0.05$ FDR corrected), as well as frontal regions. In late-life, decreasing BMI was also associated with increased cortical thinning, including right caudal middle frontal cortex (0.014 mm kg^{-1} m^{-2} (CI = 0.006–0.023, $P < 0.05$ FDR corrected).
CONCLUSIONS: The pattern of cortical thinning—in association with increasing BMI at both midlife and late-life—is consistent with known obesity-related dementia risk. Increased cortical thinning in association with decreasing BMI at late-life may help explain the 'obesity paradox', where high BMI in midlife appears to be a risk factor for dementia, but high BMI in late-life appears, at times, to be protective.

International Journal of Obesity advance online publication, 31 October 2017; doi:10.1038/ijo.2017.254

INTRODUCTION

Recent evidence suggests that being overweight in midlife increases the risk of dementia by 20–30%, and being obese in midlife increases dementia risk by 60–90%, compared with individuals with normal weight.[1,2] In addition, overweight and obesity in midlife are associated with lower cognitive abilities in late life.[3] One mechanism by which obesity might amplify dementia risk is by worsening cerebral atrophy,[4] as cerebral atrophy is a feature of dementia.[5,6] In addition to brain regions found to atrophy as a normal part of the ageing process (for example, inferior frontal and lateral temporal cortex),[7] dementia is further associated with increased cortical atrophy in other brain regions, including medial temporal and posterior cingulate/precuneus cortex.[8,9] Adiposity-related inflammation may be a driver of cortical atrophy in obesity.[10]

In late-life, however, the reported relationship between overweight/obesity and dementia risk is conflicting, with several studies finding the risk for dementia increased with higher body mass index (BMI),[11] and others showing decreased risk with higher BMI.[12–15] This so-called 'obesity paradox' is puzzling, given that animal studies suggest that obesity has an even greater impact on oxidative stress and inflammatory processes in late-life.[16] However, it may be that additional factors come into play in late-life such that higher BMI may become protective against dementia risk. For example, higher BMI has been found to be protective against loss of muscle mass (sarcopenia).[17] Although sarcopenia is part of normal ageing,[18] accelerated sarcopenia is associated with increased inflammation.[19]

Another explanation for how late-life high BMI might become protective against dementia risk is the role of adipose tissue in the production of the hormone leptin and estrogens, both of which play an important role in cognitive function.[15] Overall, it appears that the relationship between BMI (but not adiposity) and brain health is multifaceted and might change across the life-course, as different factors come into play.

Therefore, we hypothesised that in late-life—and in contrast to midlife—both increasing and decreasing BMI would be associated with brain atrophy. We further hypothesised that this potential difference in brain atrophy patterns might explain why high BMI in midlife appears to be a risk factor for dementia, but high BMI in late-life appears, at times, protective.

To test our hypothesis, we investigated cortical thinning in association with BMI, as well as changes in BMI, in a sample ($n = 405$) of individuals in midlife (44–49 years), scanned with magnetic resonance imaging (1.5T) on up to three occasions over 8 years, as well as a sample ($n = 387$) of individuals in late-life (60–66 years) scanned on up to four occasions over 12 years. The longitudinal association between cortical thickness, baseline BMI and change in BMI was tested across the cortical surface as well as in 35 regions of interest (ROIs) in each hemisphere.

[1]ANU College of Engineering & Computer Science, The Australian National University, Canberra, Australia; [2]Centre for Healthy Brain Ageing, Neuropsychiatric Institute, University of New South Wales, Sydney, Australia and [3]Centre for Research on Ageing, Health and Wellbeing, The Australian National University, Canberra, Australia. Correspondence: Dr ME Shaw, ANU College of Engineering & Computer Science The Australian National University, Brian Anderson Building 115, North Rd, Canberra, ACT 2601, Australia.
E-mail: marnie.shaw@anu.edu.au
Received 4 June 2017; revised 23 August 2017; accepted 24 September 2017; accepted article preview online 10 October 2017

MATERIALS AND METHODS

Study population

Participants were sampled from the Personality and Total Health through Life (PATH) project, a large longitudinal study of ageing aimed at investigating the course of mood disorders, cognition, health and other individual characteristics across the adult lifespan (Anstey, *et al.*,[20]). PATH surveys 2551 individuals aged 60–66 years at baseline, of which 479 were scanned in the magnetic resonance imaging (MRI) sub-study, and 2530 individuals aged 40–44 years at baseline, of which 431 were scanned in the MRI sub-study. Individuals included in the MRI sub-study were compared with those excluded, to assess potential bias. It was expected that this study design would enable the detection of small-to-medium effect sizes with a power of 0.8 and alpha of 0.05 two-tailed, based on previous power estimates for a similar study design in the older group.[21]

The individuals aged 60–66 years were first scanned at baseline with up to three follow-up scans ~4 years apart with mean total follow-up time 12.2 ± 0.3 years. The individuals aged 40–44 years at baseline were first scanned at the second wave of data collection (age 44–49 years) and had up to two follow-up scans ~4 years apart with a mean total follow-up time of 8.5 ± 0.1 years. All participants were residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, and were randomly recruited through the electoral roll (enrolment to vote is compulsory for Australian citizens). The study was approved by the Australian National University Ethics Committee and all participants provided written informed consent.

The sample selection diagram (Figure 1) outlines how, of the 910 participants initially scanned, the final analysis was based on 792 individuals, after attrition and exclusions, including 387 individuals aged 60–66 years at first MRI and 405 individuals aged 44–49 years at first MRI. For individuals aged 60–66 years at first MRI, we had data for 220 individuals over 12.2 ± 0.3 years (mean follow-up time), plus 21 individuals over 8.2 ± 0.3 years, 50 individuals over 4.1 ± 0.3 years and 96 individuals with a single MRI. For individuals aged 44–49 years at first MRI, we had data for 262 individuals over 8.5 ± 0.1 years plus 42 individuals over 4.2 ± 0.2 years and 101 individuals with a single MRI scan.

Exclusions were designed to reduce potential causes of atrophy that may confound the relationship of interest (BMI-related atrophy) and to minimise the possibility of reverse causality (illness affecting BMI). On this basis, we excluded scans where individuals had epilepsy, Parkinson's disease, stroke, mild cognitive impairment and dementia. In the late-life cohort the mini mental state exam test was administered and individuals with mini mental state exam < 27 were excluded to decrease the likelihood of inclusion of participants in the preclinical stages of dementia. Further scans were excluded on the basis of failed MRI processing or outlier cortical thickness data (further details in section 2.3).

BMI and health measures

BMI (kg m^{-2}) was computed with the formula weight/height^2 based on self-report of weight and height. For waves three and four, waist circumference, as measured by an interviewer, was also available and was found to be highly correlated with BMI measurements ($r = 0.76$, $P <$ 1e-10). At each measurement, changing BMI was the difference between current and previous BMI measurements, as a percentage of the previous BMI measurement divided by the time between measurements (% change per year). The presence of systemic hypertension was defined as a mean systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg (two blood pressure readings were taken, one at the beginning and one at the end of the interview), or the use of antihypertensive medication. Physical activity (PA) was assessed by self-report. Hours of average weekly PA for three intensity categories (mild, moderate and vigorous) were estimated and combined based on the metabolic equivalents of each activity.[22] Metabolic equivalents express the energy cost of physical activities based on the ratio of the metabolic rate during a specific PA to a reference metabolic rate. Specifically, we used the formula previously used in our group, metabolic equivalents = (mild PAx1) +(moderate PAx2)+(vigorous PAx3).[23] Smoking (current), depression symptomatology (Goldberg scale), stroke status and diabetes (type 2) were assessed by self-report. We used a linear mixed effects model to measure the longitudinal association between BMI and age.

MRI scan acquisition

T1-weighted three-dimensional structural MRI scans were obtained for all volunteers using 1.5T MRI scanners. For the first two waves of data collection, MRI scans were acquired using a Philips Gyroscan ACS-NT scanner (Philips Medical Systems, Best, The Netherlands) in coronal orientation using a fast-field echo sequence. For wave 1 (baseline scan in late-life group), the repetition time (TR), echo time (TE), flip angle and slice thickness was 28.05 ms/2.64 ms/30 and 2 mm, respectively, with matrix size 256 × 256. For wave 2 (baseline scan in midlife group, 2nd scan in the late-life group), TR, TE, flip angle and slice thickness was 8.93 ms/

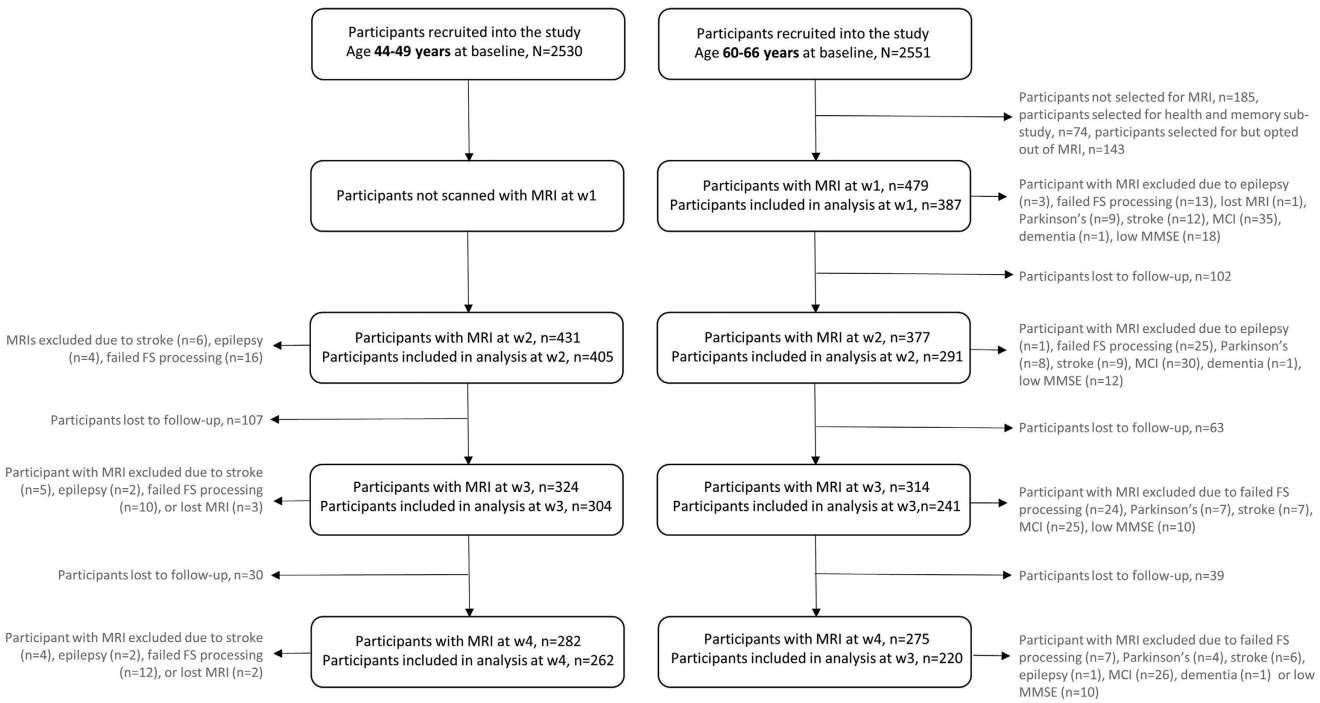

Figure 1. Sample selection process. w1 = wave 1, w2 = wave 2, w3 = wave 3, w4 = wave 4. FS = Freesurfer, MCI = mild cognitive impairment, MMSE = mini mental state exam.

3.57 ms/8 and 1.5 mm respectively, with matrix size 256 × 256. For the third wave, scans were acquired using a Siemens Espree scanner with (TR/TE/flip_angle/slice_thickness) = (1.16/4.24 ms/15/1 mm), matrix size 256 × 256 and voxel size 1 × 1 × 1 mm. For wave 4, participants were scanned on a Siemens 1.5T Espree scanner with TR, TE, flip angle and slice thickness equal to 1160 ms/4.24 ms/15 and 1mm, respectively, with matrix size 512 × 512. To account for variance owing to changes in scanner and scan parameters between waves of data collection, the thickness data were orthogonalised with respect to a scanner covariate, as outlined elsewhere in further detail.[7]

Image processing

Further image analysis was carried out using FreeSurfer v5.3, including the estimation of the cortical surfaces and the cortical thickness for each participant.[24] Processing quality control was implemented through an in-house script, which identified outlier scans based on total gray and white matter volumes. These scans were visually checked and if confirmed to have failed Freesurfer processing or have outlier mean cortical thickness (identified using Mahalanobis with χ^2 $P < 0.01$), they were removed from further analysis (numbers provided in Figure 1). We used the longitudinal FreeSurfer pipeline, where a within-subject template is created, which allows equal treatment of all input images, thus limiting processing bias associated with the use of a particular time-point as the reference image.[25] Thickness estimates were orthogonalised with respect to a categorical scanner covariate, to remove scanner-specific variance that might confound estimates of age-related change in thickness. A general linear model within MATLAB (2012b, The MathWorks, Natick, MA, USA) was used to estimate and remove variance specific to this covariate, as outlined in full detail elsewhere.[7] Next, surface-based spatial smoothing was applied to the wave-corrected data (12 mm FWHM).

Linear mixed effects modelling within and across the cortical surface

We used linear mixed effects modelling, as implemented recently in Freesurfer, to investigate the longitudinal association between BMI and cortical thickness.[26] Cortical thickness was assessed point-wise across the cortex as well as averaged within 68 ROIs. ROIs were defined based on the Desikan-Killiany atlas.[27] Linear mixed effects is a standard analysis approach for longitudinal data and correctly models the mean and covariance structure of repeated measures within participants and across assessments. The temporal covariance structure was assumed to be shared across vertices within a homogenous region of interest, as this approach has been shown to offer a substantial gain in statistical power and repeatability of findings.[28]

For the first analysis, cortical thickness was modelled as a linear function of baseline BMI with different slopes for the midlife and late-life groups, controlling for age, age^2, sex, education, hypertension, diabetes, smoking, PA and intra-cranial volume. This analysis establishes the association between cortical thickness and BMI at the time of the baseline scan. Sex interaction effects were tested in brain regions showing significant associations between baseline BMI and cortical thickness.

For the second analysis, cortical thickness was modelled as a linear function of changing BMI (decreasing and increasing annual percent change in BMI), controlling for BMI at baseline, age, age^2, sex, diabetes status, depression, smoking, education, hypertension, PA and intra-cranial volume. Age, age^2, baseline BMI and changing BMI (increasing and decreasing) were modelled with different slopes for each group. For both analyses, subject-specific intercept and age were modelled as random effects. Results were considered significant if they reached $P < 0.05$, corrected with false discovery rate (FDR), across 34 ROIs in each hemisphere.[29] Because only a select number of ROIs were compared between groups, we did not correct for multiple comparisons for the between-group comparisons. Surface-based analyses were also carried out for all points over the whole cortical surface (~300 K vertices).

RESULTS

Demographic and clinical characteristics of the participants at the time of their first MRI are presented in Table 1 and Figure 1. Midlife individuals in the whole PATH sample did not differ from those in the study sample in mean age, BMI, race, gender balance, the percentage with diabetes or the percentage of current smokers, although the study sample had slightly fewer years of education ($P < 0.02$) and a smaller proportion with hypertension ($P < 0.005$). Late-life individuals in the whole PATH sample did not differ from those in the study sample in mean age, BMI, race, gender balance or the percentage with diabetes, although the study sample had more years of education ($P < 0.001$), higher mean mini mental state exam ($P <$ 1e-7) and a smaller proportion of current smokers ($P < 0.01$).

Different pattern of weight change at mid- and late-life

Patterns of weight change in midlife and in late-life were different in that a greater percentage of midlife individuals gained weight and a smaller percentage lost weight, compared with late-life individuals ($P < 0.008$). The longitudinal association between BMI and age showed significantly increasing BMI with age in the group of 44–49 year olds ($B = 0.08$ kg m^{-2} per year, F(322) = 19.2, $P <$ 1e-5). In this midlife group, 211 individuals (50%) gained weight, with a mean annual percentage change in BMI (APC_BMI) of 1.1 ± 1.0% per year. 115 (28%) lost weight (mean APC_BMI = − 1.0 ± 1.0% per year). In the late-life group there was a trend towards increasing BMI with age ($B = 0.02$ kg m^{-2} per year, F(277) = 2.7, $P < 0.10$), with 165 individuals (42%) gaining weight (mean APC_BMI 0.6 ± 0.7%

Table 1. Demographic and health characteristics for individuals within the whole PATH sample compared with the study sample for midlife individuals (44–49 years, wave 2) as well as late-life individuals (60–66 years, wave 1)

	Midlife		*Late-life*	
	Path sample	*Study sample*	*Path sample*	*Study sample*
N	2354	405	2550	387
Female, *n* (%)	1251 (53%)	219 (54%)	1234 (48%)	188 (49%)
Age, years (s.d.)	47.1 (1.4)	47.2 (1.4)	63.0 (1.5)	63.1 (1.4)
Age range	44.1–50.2	44.7–49.8	60.2–66.8	60.3–66.0
Education, years (s.d.)	14.8 (2.2)	14.5 (2.4)[a]	13.8 (2.8)	14.3 (2.4)[a]
MMSE, score (s.d.)	–	–	29.1 (1.5)	29.5 (0.7)[a]
hypertension, *n* (% with)	636 (27%)	85 (21%)[a]	1606 (63%)	230 (59%)
BMI (kg m^{-2}), mean (s.d.)	26.9 (5.1)	27.2 (4.8)	26.8 (4.8)	26.3 (4.2)
Caucasian, *n* (%)	2236 (95%)	389 (96%)	2448 (96%)	373 (96%)
Diabetes, *n* (%)	70 (3%)	8 (2%)	193 (8%)	30 (8%)
Smoke, *n* (%)	280 (18%)	61 (15%)	285 (11%)	27 (7%)[a]

Abbreviations: BMI, body mass index; MMSE, mini mental state exam. [a]Denotes significant differences (see Results for list).

per year) and 136 (34%) losing weight (mean APC_BMI −0.7 ± 0.9% per year).

Baseline BMI is associated with cortical thickness in late-life but not at midlife

There was no association between BMI at baseline and cortical thickness at midlife, although a region in right medial superior frontal cortex showed a trend ($P < 0.10$) toward an association between baseline BMI and cortical thickness. For late-life individuals, a higher BMI at baseline was associated with decreased cortical thickness in a number of regions. In total, there were seven regions where the association between BMI at baseline and cortical thickness was more significant in the late-life group, compared with the midlife group ($P < 0.05$), most prominently bilateral entorhinal cortex and bilateral cingulate (Table 2). These regions did not show an interaction between sex and BMI at baseline, in association with cortical thickness.

Increasing BMI is associated with increased cortical thinning at midlife and at late-life

Increasing BMI was associated with increased cortical thinning in both the midlife and late-life groups. At midlife, a significant association between increasing BMI and cortical thinning was observed in left posterior cingulate (Figure 2, Table 3). The association corresponded to a decrease of 0.014 mm APC_BMI^{-1} (confidence interval; CI = 0.004–0.023, $P < 0.05$ FDR corrected). This corresponds to ~0.5% of baseline cortical thickness for every 1% annual change in BMI. In late-life, cortical thinning was observed in association with increasing BMI, most prominently in right supramarginal gyrus (0.010 mm APC_BMI^{-1}, CI = 0.005–0.016, $P < 0.05$ FDR corrected), but also in right precuneus and bilateral middle frontal cortex, as well as right insula and right superior frontal cortex (Figure 2, Table 3). The late-life group showed more cortical thinning in right supramarginal cortex ($P < 0.04$) and right insula ($P < 0.05$), compared with the midlife group.

Decreasing BMI is associated with increased cortical thinning in late-life only

For the late-life group, significantly more cortical thinning was observed in association with decreasing BMI, compared with the midlife group. For example, cortical thinning in right caudal middle frontal cortex was 0.014 mm APC_BMI^{-1} (CI = 0.006–0.023, $P < 0.05$ FDR corrected). Other significant regions included left caudal middle frontal cortex and left frontal pole. Six other regions showed more cortical thinning in the late-life group compared with the midlife group ($P < 0.05$) (Figure 3, Table 3).

DISCUSSION

We found that increasing BMI was associated with increased cortical atrophy in midlife and continuing at late-life. Consistent with this, we found that a higher BMI was associated with thinner entorhinal and cingulate cortex at late-life. Interestingly, decreasing BMI was also associated with cortical atrophy, but only in the late-life group. We outline below, how these different BMI-related atrophy patterns might help explain the 'obesity paradox', that is, why higher BMI is associated with increased risk of AD and cognitive decline at midlife, yet sometimes appears protective in late-life.

Increasing BMI at midlife, and higher baseline BMI at late-life, is associated with thinner cortex in AD vulnerable regions (entorhinal and posterior cingulate cortex)

We observed an association between increasing BMI and cortical thinning in left posterior cingulate at midlife ($P < 0.05$, FDR corrected, Figure 2, Table 3). Consistent with this, we observed—in late-life—decreased cortical thickness in association with baseline BMI in bilateral entorhinal and cingulate cortex (Table 2). To explain, consider that the association in the midlife group corresponded to a decrease in thickness of the left posterior cingulate cortex by 0.014 mm for every 1% annual increase in BMI. Given the thickness of the posterior cingulate was 2.59 mm at baseline, this change corresponds to 0.5%, which is close to the annual age-related cortical thinning measured in this region (0.4%). Thus, a midlife individual with a 1% change in BMI per year is expected to experience approximately twice the amount of cortical thinning in this region, compared with an individual with no change in BMI. In this way, we would expect a late-life individual, with higher BMI, to have thinner left posterior cingulate cortex.

Posterior cingulate has been extensively studied as one of the first brain regions affected in AD and has been shown to have abnormal metabolism,[30] abnormal connectivity[31] and reduced volume.[32] AD-related change in posterior cingulate cortex is thought to affect learning and memory, key features of early Alzheimer's disease.[30] Entorhinal volume has also been found to be a particularly sensitive predictor of AD, with one study demonstrating that entorhinal volume predicted individuals who were destined to develop dementia with 84% accuracy.[33] Therefore, decreased cortical thickness in these regions, in association with higher baseline BMI at late-life or increasing BMI at midlife, is consistent with the known increased risk of AD with increased/increasing BMI at midlife.

Table 2. Association between baseline BMI (kg m^{-2}) and cortical thickness (mm) for both the midlife and late-life groups, controlling age, age^2, sex, diabetes status, depression, smoking, hypertension, physical activity and intra-cranial volume (ICV)

Region	*Association between BMI and cortical thickness at baseline*				
	Midlife		*Late-life*		*Late-life vs midlife*
	mm kg^{-1} m^2	*CI*	*mm kg^{-1} m^2*	*CI*	
R. rostral ACC	−0.001	(0.004, −0.005)	−0.008	(−0.003, −0.013)[a]	0.024
R. PCC	−0.001	(0.002, −0.004)	−0.006	(−0.002, −0.010)[a]	0.028
R. entorhinal	−0.002	(0.003, −0.007)	−0.011	(−0.006, −0.017)[a]	0.033
L. rostral ACC	−0.002	(0.002, −0.006)	−0.008	(−0.002, −0.013)[a]	0.039
L. PCC	−0.001	(0.002, −0.004)	−0.007	(−0.003, −0.011)[a]	0.011
L. entorhinal	−0.001	(0.004, −0.006)	−0.008	(−0.003, −0.014)[a]	0.012
L. insula	0.000	(0.002, −0.003)	−0.005	(−0.002, −0.009)[a]	0.031

Abbreviations: ACC, anterior cingulate cortex; CI, confidence interval, L./R., left/right; PCC, posterior cingulate cortex. Coefficients correspond to mm for every BMI unit (kg m^{-2}). [a]Denotes $P < 0.05$, FDR corrected.

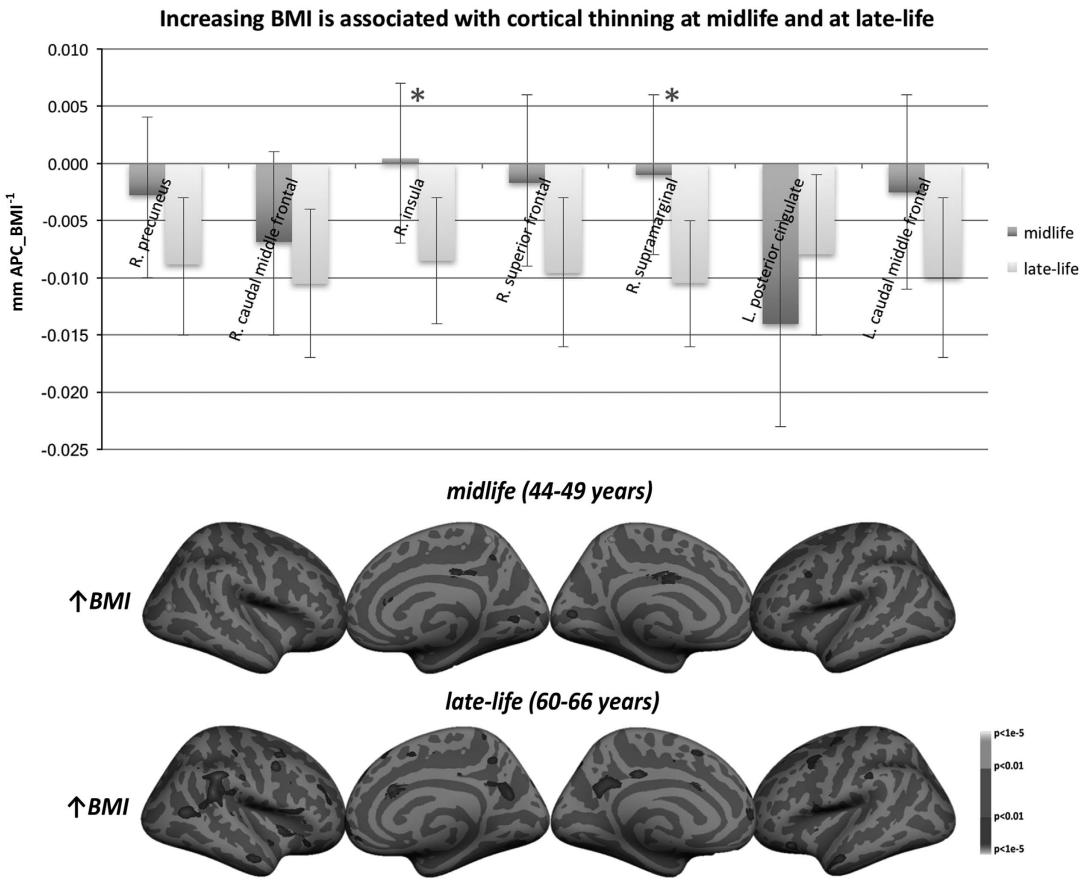

Figure 2. Increasing BMI is associated with cortical thinning at midlife and at late-life. TOP: Longitudinal association between mean cortical thickness and increasing BMI for midlife individuals (blue) compared with late-life individuals (orange), within regions of interest (ROIs). Only ROIs where BMI-related longitudinal thinning was significant ($P < 0.05$, FDR corrected) in one of the two groups are shown. * denotes significant differences between groups ($P < 0.05$). L./R. = left/right. These results are listed in Table 3. Bottom: significance maps of the longitudinal association between increasing BMI and cortical thinning for midlife (top) and late-life (bottom) individuals, controlling for baseline BMI, age, age^2, sex, diabetes status, depression, smoking, hypertension, physical activity and ICV ($P < 0.01$, uncorrected). A full colour version of this figure is available at the *International Journal of Obesity* journal online.

Putative mechanisms for different BMI-related cortical thinning patterns mid- and late-life

In late-life, increased cortical thinning was also observed in association with decreasing BMI. Compared with the midlife group, more cortical thinning in association with decreasing BMI was observed in the late-life group in a number of regions across the frontal cortex bilaterally, as well as left precuneus (Figure 3, Table 3). In the late-life group, both increasing and decreasing BMI could result in inflammation-related brain atrophy, as outlined below.

A previous longitudinal study in men showed body mass increases from age 20–70 years, primarily owing to increased fat mass (adiposity), whereas body mass decreases after age 70 years, primarily owing to the loss of fat-free mass.[18] Importantly, accelerated loss of fat-free mass (sarcopenia) often co-occurs with an increase in fat mass.[34] We propose that, in the late-life individuals in our study, those with increasing BMI more likely have increased adipose tissue, and at least some of the individuals with decreasing BMI may have accelerating sarcopenia, with associated increase in fat mass. Both conditions could affect cortical atrophy directly via systemic low-grade inflammation associated with adipose tissue,[19,35] for example, or indirectly via associated medical conditions. Here we have controlled for hypertension, diabetes and PA such that an indirect effect is less likely. Inflammation is a more likely mechanism, given that adipose tissue is the largest endocrine organ in the human body and secretes hormones, cytokines and growth factors which cross the blood–brain barrier and contribute to homeostasis.[36] Inflammation-related brain atrophy may reflect, in addition to loss of neurons, loss of glial cells and axons[37] as well as cellular shrinkage and reduced dendritic arborisation.[38]

Strengths and limitations

One limitation of the current study is the fact that our study sample is not representative of the general population. We used a random sample from a large group of study participants but those individuals had a relatively high level of education and social-economic status,[20] which may result in lower atrophy estimates than would be expected in a less educated cohort. Furthermore, as is common with large, longitudinal imaging studies, different scanners and different scan parameters were used across waves of data collection (outlined in methods), although a robust and published method was used to effectively control for these effects and a test was done to ensure cortical thickness measurements were not biased by scanner model.[7,39]

A further limitation was the use of self-report for BMI, which may not be accurate, although we did have waist circumference measurements (measured by an interviewer) at two waves of data collection, and these were highly correlated with our BMI measurements. Although BMI grossly reflects total adipose tissue depots during adulthood,[10] better methods of quantifying adipose tissue and it is composition are needed, including the

Table 3. Longitudinal association between increasing/decreasing BMI (annual percent change) and cortical thickness (mm) for both the midlife and late-life groups, controlling for baseline BMI, age, age^2, sex, diabetes status, depression, smoking, hypertension, physical activity and intra-cranial volume (ICV)

		Midlife		*Late-life*		*Late-life* vs *midlife*
	Region	*mm APC_BMI^{-1}*	*CI*	*mm APC_BMI^{-1}*	*CI*	P-*value*
Association between increasing BMI and cortical thinning						
Significant in late-life	R. precuneus	−0.003	(0.004, −0.010)	−0.009	(−0.003, −0.015)[a]	0.181
	R. caudal middle frontal	−0.007	(0.001, −0.015)	−0.011	(−0.004, −0.017)[a]	0.495
	R. insula	0.000	(0.007, −0.007)	−0.009	(−0.003, −0.014)[a]	0.055
	R. superior frontal	−0.002	(0.006, −0.009)	−0.010	(−0.003, −0.016)[a]	0.112
	R. supramarginal	−0.001	(0.006, −0.008)	−0.010	(−0.005, −0.016)[a]	0.038
	L. caudal middle frontal	−0.003	(0.006, −0.011)	−0.010	(−0.003, −0.017)[a]	0.173
Significant in midlife	L. posterior cingulate	−0.014	(−0.005, −0.023)[a]	−0.008	(−0.001, −0.015)	0.288
Association between decreasing BMI and cortical thinning						
Late-life > midlife	R. pars orbitalis	0.004	(0.016, −0.009)	−0.013	(−0.003, −0.023)	0.044
	R. pars triangularis	0.007	(0.018, −0.003)	−0.011	(−0.002, −0.020)	0.009
	R. rostral middle frontal	0.008	(0.017, −0.002)	−0.009	(−0.002, −0.017)	0.005
	R. caudal middle frontal	−0.003	(0.007, −0.014)	−0.014	(−0.006, −0.023)[a]	0.100
	L. precuneus	0.006	(0.015, −0.002)	−0.006	(0.001, −0.013)	0.028
	L. caudal middle frontal	0.002	(0.012, −0.009)	−0.014	(−0.006, −0.023)[a]	0.022
	L. frontal pole	−0.004	(0.012, −0.021)	−0.025	(−0.012, −0.038)[a]	0.052
	L. lateral orbitofrontal	0.002	(0.012, −0.008)	−0.011	(−0.003, −0.019)	0.053
	L. rostral middle frontal	0.002	(0.011, −0.008)	−0.011	(−0.003, −0.019)	0.043

Abbreviations: CI, confidence interval; L.R., left/right. Coefficients correspond to mm for every one percent annual change in BMI (mm APC_BMI^{-1}). [a]Denotes $P < 0.05$, FDR corrected.

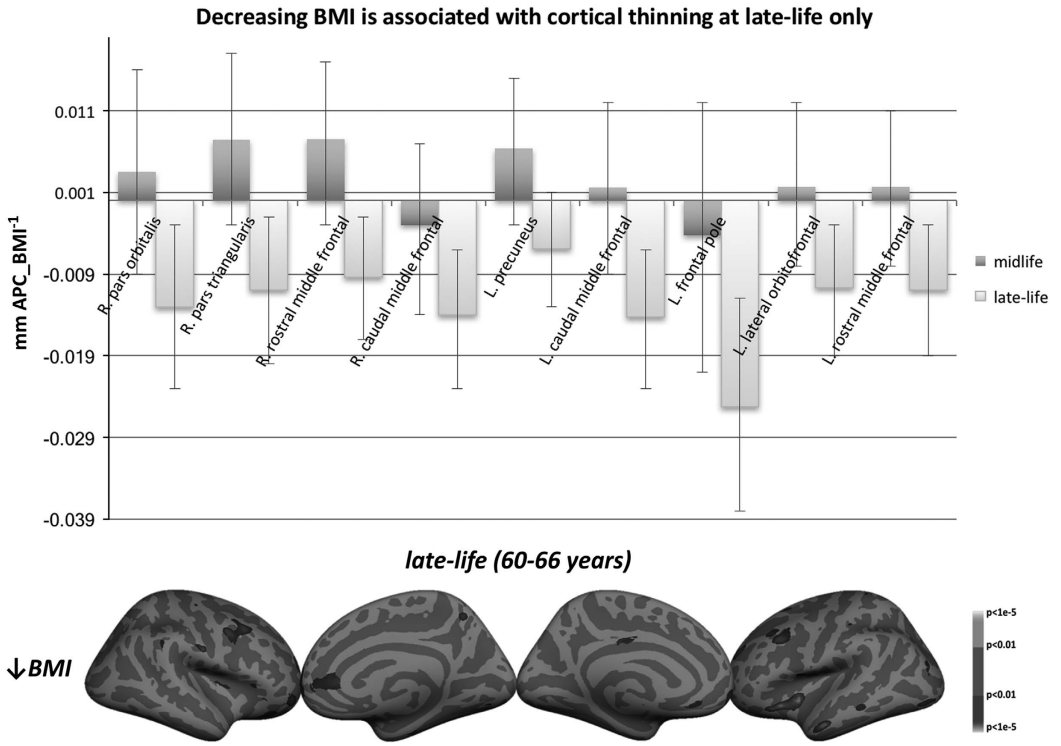

Figure 3. Decreasing BMI is associated with cortical thinning at late-life only. Top: longitudinal association between mean cortical thickness and decreasing BMI for midlife individuals (blue) compared with late-life individuals (orange), within regions of interest (ROIs). All ROIs shown, except for right caudal middle frontal cortex, had significantly more longitudinal thinning in the late-life group, compared with the midlife group ($P < 0.05$). L./R. = left/right. These results are listed in Table 3. Bottom: significance maps of the longitudinal association between decreasing BMI and cortical thinning for late-life individuals, controlling for baseline BMI, age, age^2, sex, diabetes status, depression, smoking, hypertension, physical activity and ICV ($P < 0.01$, uncorrected). There was no association between decreasing BMI and cortical thinning in the midlife group. A full colour version of this figure is available at the *International Journal of Obesity* journal online.

measurement of white versus brown adipose tissue and adipokine levels.

Conclusions

The goal of our research is to identify and quantify risk factors that potentially impact brain atrophy, with the overarching goal of reducing the risk of cognitive decline and dementia over the lifespan. Obesity is a known risk factor for brain atrophy and cognitive decline. Here we have shown that the risk profile associated with BMI may change over the lifespan. We found that brain atrophy was associated with increasing BMI at both midlife and at late-life and, consistent with this, that late-life individuals with higher BMI had increased brain atrophy compared with those with normal BMI. Interestingly, we further identified brain atrophy associated with decreasing BMI, but only in the late-life group. Understanding how the risk profile associated with BMI changes over the lifespan—in terms of cognitive health—may be important for risk reduction measures.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We are grateful to Peter Butterworth, Simon Easteal, Helen Christensen, Patricia Jacomb, Karen Maxwell and the PATH interviewers. The study was supported by NHMRC grant No. 973302, 179805, 350833 157125, ARC grant No. 130101705 and the Dementia Collaborative Research Centres. Nicolas Cherbuin is funded by ARC Fellowship No. 12010227 and Kaarin Anstey by and NHMRC Fellowship No.1002560. This research was partly undertaken on the National Computational Infrastructure (NCI) facility in Canberra, Australia, which is supported by the Australian Commonwealth Government.

REFERENCES

1 Anstey K, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev* 2011; **12**: e426–e437.
2 Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the united states and china. *Obesity* 2013; **21**: E51–E55.
3 Dahl AK, Hassing LB, Fransson EI, Gatz M, Reynolds CA, Pedersen NL. Body mass index across midlife and cognitive change in late life. *Int J Obes* 2013; **37**: 296–302.
4 Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH *et al.* Brain structure and obesity. *Hum Brain Map* 2010; **31**: 353–364.
5 Weinstein G, Beiser AS, DeCarli C, Au R, Wolf PA, Seshadri S. Brain imaging and cognitive predictors of stroke and Alzheimer disease in the Framingham Heart Study. *Stroke* 2013; **44**: 2787–2794.
6 Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS *et al.* Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013; **12**: 207–216.
7 Shaw ME, Sachdev PS, Anstey KJ, Cherbuin N. Age-related cortical thinning in cognitively healthy individuals in their 60s: the PATH Through Life study. *Neurobiol Aging* 2016; **39**: 202–209.
8 Pacheco J, Goh JO, Kraut MA, Ferrucci L, Resnick SM. Greater cortical thinning in normal older adults predicts later cognitive impairment. *Neurobiol Aging* 2015; **36**: 903–908.
9 Dickerson B, Stoub T, Shah R, Sperling R, Killiany R, Albert M *et al.* Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology* 2011; **76**: 1395–1402.
10 Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: a link between obesity and dementia? *Lancet Neurol* 2014; **13**: 913–923.
11 Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Int Med* 2003; **163**: 1524–1528.
12 Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth W *et al.* Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 2009; **66**: 336–342.
13 Dahl AK, Löppönen M, Isoaho R, Berg S, Kivelä SL. Overweight and obesity in old age are not associated with greater dementia risk. *J Am Geriatr Soc* 2008; **56**: 2261–2266.
14 Hughes T, Borenstein A, Schofield E, Wu Y, Larson E. Association between late-life body mass index and dementia The Kame Project. *Neurology* 2009; **72**: 1741–1746.
15 Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. *J Am Geriatr Soc* 2008; **56**: 111–116.
16 Bailey-Downs LC, Tucsek Z, Toth P, Sosnowska D, Gautam T, Sonntag WE *et al.* Aging exacerbates obesity-induced oxidative stress and inflammation in perivascular adipose tissue in mice: a paracrine mechanism contributing to vascular redox dysregulation and inflammation. *The J Gerontol A Bio Sci Med Sci* 2013; **68**: 780–792.
17 Yu R, Wong M, Leung J, Lee J, Auyeung TW, Woo J. Incidence, reversibility, risk factors and the protective effect of high body mass index against sarcopenia in community-dwelling older Chinese adults. *Geriatr Gerontol Int* 2014; **14**: 15–28.
18 Jackson AS, Janssen I, Sui X, Church TS, Blair SN. Longitudinal changes in body composition associated with healthy ageing: men, aged 20–96 years. *Br J Nutr* 2012; **107**: 1085–1091.
19 Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *The Am J Med* 2006; **119**: 526. e9-. e17.
20 Anstey KJ, Christensen H, Butterworth P, Easteal S, Mackinnon A, Jacomb T *et al.* Cohort Profile: The PATH through life project. *Int J Epidemiol* 2012; **41**: 951–960.
21 Cherbuin N, Sargent-Cox K, Fraser M, Sachdev P, Anstey K. Being overweight is associated with hippocampal atrophy: the PATH Through Life Study. *Int J Obes* 2015; **39**: 1509.
22 Jette M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990; **13**: 555–565.
23 Lamont AJ, Mortby ME, Anstey KJ, Sachdev PS, Cherbuin N. Using sulcal and gyral measures of brain structure to investigate benefits of an active lifestyle. *NeuroImage* 2014; **91**: 353–359.
24 Fischl B. FreeSurfer. *Neuroimage* 2012; **62**: 774–781.
25 Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage* 2012; **61**: 1402–1418.
26 Bernal-Rusiel JL, Greve DN, Reuter M, Fischl B, Sabuncu MR. Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage* 2013; **66**: 249–260.
27 Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006; **31**: 968–980.
28 Bernal-Rusiel JL, Reuter M, Greve DN, Fischl B, Sabuncu MR. Spatiotemporal linear mixed effects modeling for the mass-univariate analysis of longitudinal neuroimage data. *NeuroImage* 2013; **81**: 358–370.
29 Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002; **15**: 870–878.
30 Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 1997; **42**: 85–94.
31 Zhou Y, Dougherty JH, Hubner KF, Bai B, Cannon RL, Hutson RK. Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimer's Dement* 2008; **4**: 265–270.
32 Pengas G, Hodges JR, Watson P, Nestor PJ. Focal posterior cingulate atrophy in incipient Alzheimer's disease. *Neurobiol Aging* 2010; **31**: 25–33.
33 Killiany R, Hyman B, Ta Gomez-Isla, Moss M, Kikinis R, Jolesz F *et al.* MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology* 2002; **58**: 1188–1196.
34 Prado C, Wells J, Smith S, Stephan B, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. *Clin Nutr* 2012; **31**: 583–601.
35 Samaras K, Lutgers HL, Kochan NA, Crawford JD, Campbell LV, Wen W *et al.* The impact of glucose disorders on cognition and brain volumes in the elderly: the Sydney Memory and Ageing Study. *Age* 2014; **36**: 977–993.
36 Gustafson D. Adiposity indices and dementia. *Lancet Neurol* 2006; **5**: 713–720.
37 Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes* 2014; **63**: 2244–2252.
38 Foley JM, Salat DH, Stricker NH, McGlinchey RE, Milberg WP, Grande LJ *et al.* Glucose dysregulation interacts with APOE-$\in$ 4 to potentiate temporoparietal cortical thinning. *Am J Alzheimer's Dis Dement* 2016; **31**: 76–86.
39 Shaw ME, Abhayaratna WP, Sachdev PS, Anstey KJ, Cherbuin N. Cortical thinning at midlife: the PATH through life study. *Brain Topogr* 2016; **29**: 875–884.