TITLE

Plasma amyloid-beta homeostasis is associated with Body Mass Index and weight-loss in people with overweight and obesity

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RUNNING TITLE

Plasma Aβ is linked to BMI and weight-loss

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ABSTRACT

BACKGROUND: Obesity is linked to a higher incidence of Alzheimer's disease (AD). Studies show that plasma amyloid-β (Aβ) dyshomeostasis, particularly 42/40 ratio indicates heightened risk of developing AD. However, the relationship between body mass index (BMI) and circulating plasma Aβ have not been extensively studied.

OBJECTIVE: We hypothesised that people with a high BMI have altered plasma Aβ homeostasis compared with people with a lower BMI. We also tested whether lowering BMI by calorie-restriction normalises plasma concentrations of Aβ.

METHODS: The plasma concentrations of Aβ40, Aβ42 and Aβ42/40 ratio were measured in 106 participants who were classified as either lean, overweight, and obese, based on their BMI. 12 overweight/obese participants from the cohort of 106 individuals, were thereafter subjected to a 12-week calorie-restriction weight-loss program. We then tested whether the decreased BMI shows any correlation with plasma Aβ levels.

RESULTS: Obese participants showed significantly lower mean plasma Aβ42/40 ratio compared to lean (17.54%, $p<0.0001$) and overweight participants (11.76%, $p<0.0001$). The weight-loss regimen decreased BMI by an average of 4.148%, and was associated with a 6.5% decrease in plasma Aβ40 ($p=0.0425$). However, weight loss showed negligible correlations with plasma Aβ40, Aβ42 and Aβ42/40 ratio.

CONCLUSION: Obesity is associated with aberrant plasma Aβ homeostasis which may be associated with an increased risk for AD. Weight-loss shows some influence of Aβ, but further studies are required to elucidate the underlying mechanisms of how obesity induces plasma Aβ dyshomeostasis and the complete effect of weight-loss on Aβ metabolism.

KEYWORDS

Amyloid-beta, Body Mass Index, Alzheimer's Disease, Obesity

INTRODUCTION

Alzheimer's disease (AD), the most common form of dementia, is characterised by progressive cognitive decline and the abnormal deposition of amyloid-β (Aβ) in the brain parenchyma [1]. A significant risk factor for AD is obesity, which is defined as body mass index (BMI) being ≥30 kg/m^2 [2, 3]. Obesity in people aged between 40-45 years has been associated with a three-fold higher risk of developing AD in later-life [4]. Additionally, obesity is reported to significantly accelerate the onset of AD and double the likelihood of Aβ deposition in the brain [5, 6]. These data collectively suggest that an increased BMI may have a severe impact on cerebral Aβ overload, AD onset and progression. However, the exact underlying mechanisms linking obesity with AD remain unknown.

Many studies have evaluated plasma levels of Aβ40 and Aβ42 as predictors of AD or cognitive decline [7]. Recent findings show that the dyshomeostasis of plasma Aβ, particularly low plasma Aβ42/40 ratio can predict the risk of AD at an accuracy of ~90% [8-15]. However, few studies to date have investigated the association between obesity and plasma Aβ homeostasis. Studies in otherwise healthy individuals reported that obesity and increased fat mass are significantly associated with elevated plasma abundance of Aβ40 and Aβ42 [16, 17]. However, no previous studies have extensively considered the possible relationship between BMI and the levels circulating Aβ.

Therefore, in the present study, we investigated whether BMI shows any significant associations with plasma Aβ homeostasis. Furthermore, we tested whether the reduction of BMI in overweight and obese individuals through a calorie restriction weight-loss regime modulates plasma Aβ homeostasis. The outcomes of this study may provide new insights into the mechanisms whereby obesity increases brain amyloidosis and risk of AD and may offer potential preventative opportunity with weight-loss.

MATERIALS AND METHODS

PARTICIPANTS

To investigate the association between BMI and plasma Aβ homeostasis, we recruited 106 people who either had a normal, overweight, or obese BMI. BMI cut-offs were defined according to the World Health Organisation: lean weight as 18.50-24.99 kg/m^2, overweight as 25.00-29.99 kg/m^2, and

obese as ≥30.00 kg/m^2 [18]. No participants had an underweight BMI (≤18.50 kg/m^2). Individuals with APOE2/E2 genotype, history of cardiovascular disease or used antidiabetic medication were excluded from the study. This study was approved by the Ethics Committee of Royal Perth Hospital (EC 2010/074), a national ethics committee (Bellberry Ltd, Eastwood, South Australia, 2014-03-151) and Curtin University (HRE2021-0192). Informed consent was obtained from each participant.

SAMPLE COLLECTION AND STUDY DESIGN

After a 14-hour fast, baseline whole venous blood was collected in EDTA tubes from all 106 participants and immediately centrifuged at 1500 x *g* for 15 min at 4^{o}C to obtain plasma. Plasma was collected and stored at –80^{o}C for future evaluation. All participants had their weight and height recorded for their BMI calculation.

WEIGHT LOSS PROGRAM

Following the plasma sample and BMI data collection, 12 of the 106 participants who were overweight and obese participants entered a 12-week calorie restriction weight loss program as reported previously [19]. During this weight loss regime, the participants' caloric intake was restricted to achieve a deficit of ~1440 kJ per day compared to their diets before the commencement of weight loss. Dietary intake was evaluated for energy and major nutrients by FoodWorks 2007 (Xyris Software, Brisbane, Australia). All participants were reviewed fortnightly and requested to maintain their usual level of physical activity. All dietary assessments and recommendations were conducted by a registered dietician. After completing the weight loss program, fasting plasma was collected, and BMI was recorded from the 12 participants.

QUANTIFICATION OF PLASMA AB40 AND AB42

Plasma concentrations of Aβ40 and Aβ42 were measured at baseline (*n*=106) and after the 12-week weight loss (*n*=12) using ELISA (Wako Chemical, Tokyo, Japan), according to the manufacturer's instruction. Briefly, samples were prepared in a 1:4 dilution with the kit provided diluent. All samples

and kit-provided standards were loaded onto the antibody coated microplate and incubated overnight at 4°C. Following incubation, HRP-conjugated monoclonal antibody was added to the appropriate wells, and plates were incubated in the dark. Plates where Aβ40 was being quantified were incubated for 2 hours, whilst plates where Aβ42 were being quantified were incubated for 1 hour. Subsequently, 100 µL TMB was added to each well. The plates were incubated for a further 30 minutes in the dark, and STOP solution was added before the absorbance was measured at 450 nm using EnSpire™ Multimode Plate Reader (PerkinElmer, Waltham, MA, USA).

STATISTICAL ANALYSIS

Statistical analyses were performed using GraphPad Prism 9.3.1 for Windows (GraphPad Software, CA, USA) and IBM SPSS Statistics for Windows, Version 27.0. (IBM Corp, NY, USA). The distribution of all variables was assessed by D'Agostino and Shapiro-wilk normality test. Unpaired t tests were used to compare variables of the three BMI groups. For the calorie restriction part of the study, paired t tests were used to compare the difference from baseline to week-12. Where data was not normally distributed, changes were analysed using the Wilcoxon test. For correlation analyses, we used Pearson or Spearman correlation coefficient tests depending on the data normality as well as principal component analysis (PCA). Where indicated, univariate regression model was used to adjust data for age, age squared and sex. Significance was defined at the $p<0.05$.

RESULTS

The characteristics of the cohort are summarised in Table 1. Overall, participants were aged between 18 to 66 years. The average age of obese BMI group was significantly greater compared to lean and overweight groups, whilst the average age of the lean and overweight groups was similar. Majority of the participants were male, accounting for 92.67% of the overall cohort.

BMI Groups	Lean (n=42)	Overweight (n=41)	Obese (n=23)
Age (years) (range)	32.40 ± 11.24[a] (18-54)	35.88 ± 12.66[b] (19-44)	57.57 ± 9.80[a, b] (29-66)
Gender F:M	0:42	2:39	9:14
BMI (kg/m^2) (range)	22.91 ± 1.40[c, d] (19.29-24.99)	27.25 ± 1.58[c, e] (25.00-29.88)	33.96 ± 5.12[d, e] (30.04-51.07)

Table 1: Cohort baseline characteristics

All variables are presented as mean ± SD with range.

Matching superscript lettering indicates significant difference. Alphabetical letters indicate statistical significance at $p<0.05$

The average plasma concentration of Aβ40 was significantly higher in the obese group by 41.7% compared to people with a lean BMI (Fig 1A). The average plasma concentration of Aβ40 in obese group was also significantly greater than the overweight group by 36.89%. No significant difference for plasma Aβ40 concentrations was observed between the lean and overweight groups. In contrast, plasma abundance of Aβ42 was similar across all three BMI groups (Fig 1B). The average plasma Aβ42/40 ratio in obese group was significantly lower by 32.65% compared to the lean BMI group (Fig 1C). Plasma Aβ42/40 was significantly lower in obese group by 25.74% compared to the overweight group. We also report that the mean Aβ42/40 ratio was lower by 7.05% in the overweight cohort compared to the lean group, however this did not reach statistical significance ($p=0.090$).

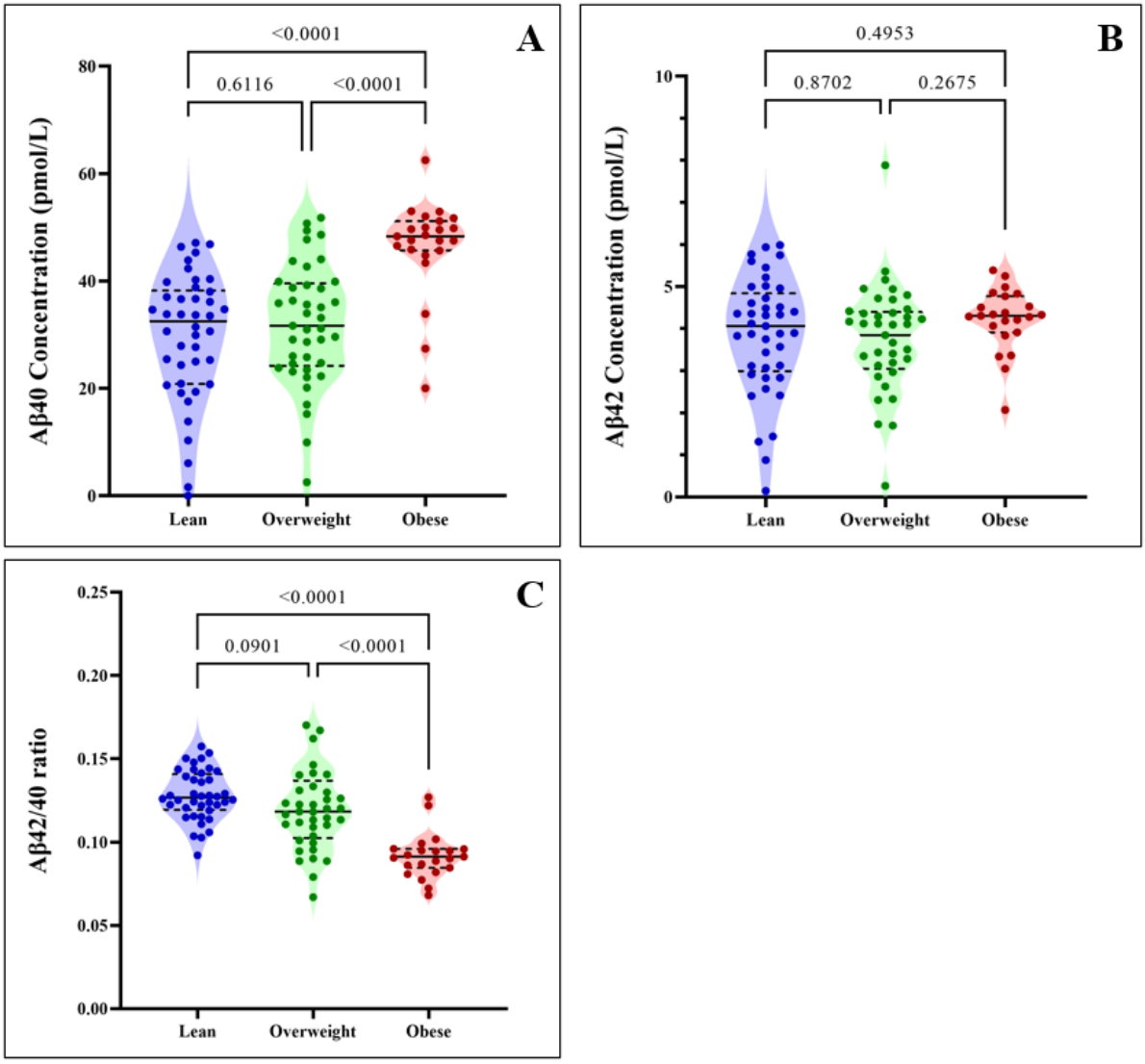

Fig. 1. Violin plot shows the plasma concentrations of A) Aβ40, B) Aβ42, and C) Aβ42/40 in people with lean, overweight, or obese BMIs. The median value is indicated by the solid line, and the quartiles are represented by the dashed lines.

To further evaluate the relationship between Aβ and BMI, we performed simple linear correlation analysis (Fig 2). BMI showed a significant positive correlation with plasma Aβ40 concentration (Fig 2A), while no significant association was observed between BMI and Aβ42 (Fig 2B). We identified a strong negative correlation between BMI and Aβ42/40 ratio (Fig 2C). Consistently, PCA loading plot also showed strong negative relationship between BMI and Aβ42/40 ratio, although Aβ40 and 42 *per se* appeared as an independent factor (Fig 2D). PCA scores plot show evident clustering of lean,

overweight and obese population with obesity showing negative correlation with Aβ42/40 ratio (Fig 2E).

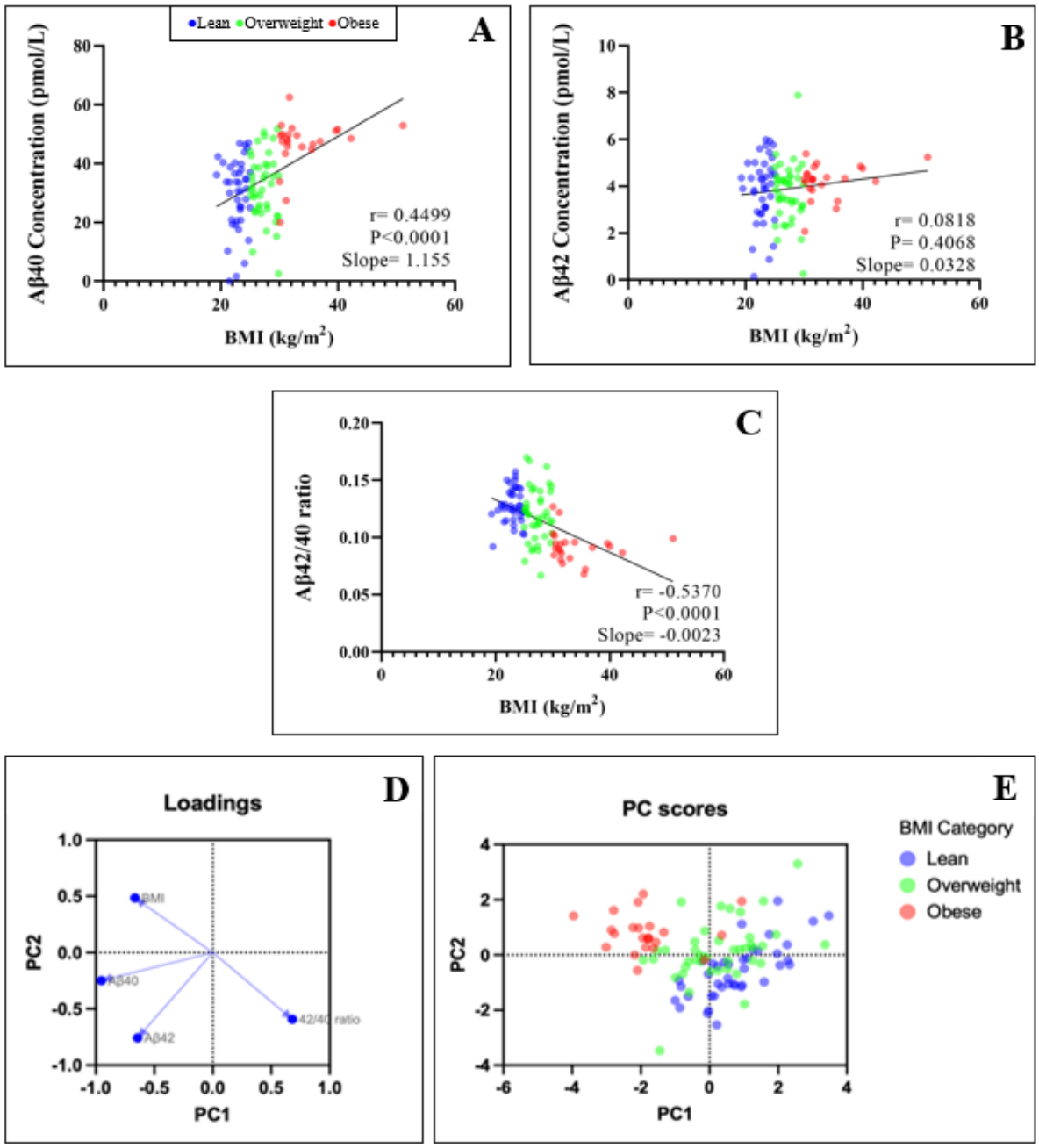

Fig. 2. The scatter plot shows the linear correlations between BMI and plasma concentrations of A) Aβ40, B) Aβ42, and C) Aβ42/40 ratio. D) Shows the PCA loading plot of BMI, Aβ40, Aβ42 and Aβ42/40, and E) PCA score plot show the scattering of Aβ42/40 in lean, overweight and obese BMI groups.

As the average age of obese group was significantly higher than lean and overweight BMI groups, and there were nearly 9-fold more men than women overall (Table 1); we used a univariate regression

model to adjust the plasma Aβ concentrations for age, age squared and sex. Following the adjustment, mean plasma Aβ40 showed increasing trend in obese group, compared to lean or overweight groups by 10.90% and 11.32%, respectively, whilst plasma Aβ40 levels were similar between lean and overweight groups (Fig 3A). The average plasma Aβ42 concentrations were not significantly different across lean, overweight and obese groups (Fig 3B). However, the relationship between BMI and Aβ42/40 ratio persisted following adjustment and showed significantly lower Aβ42/40 in the obese group, compared to both lean and overweight BMI groups by 17.54% and 11.76%, respectively. Furthermore, the Aβ42/40 ratio in overweight group was lower than the lean group (Fig 3C).

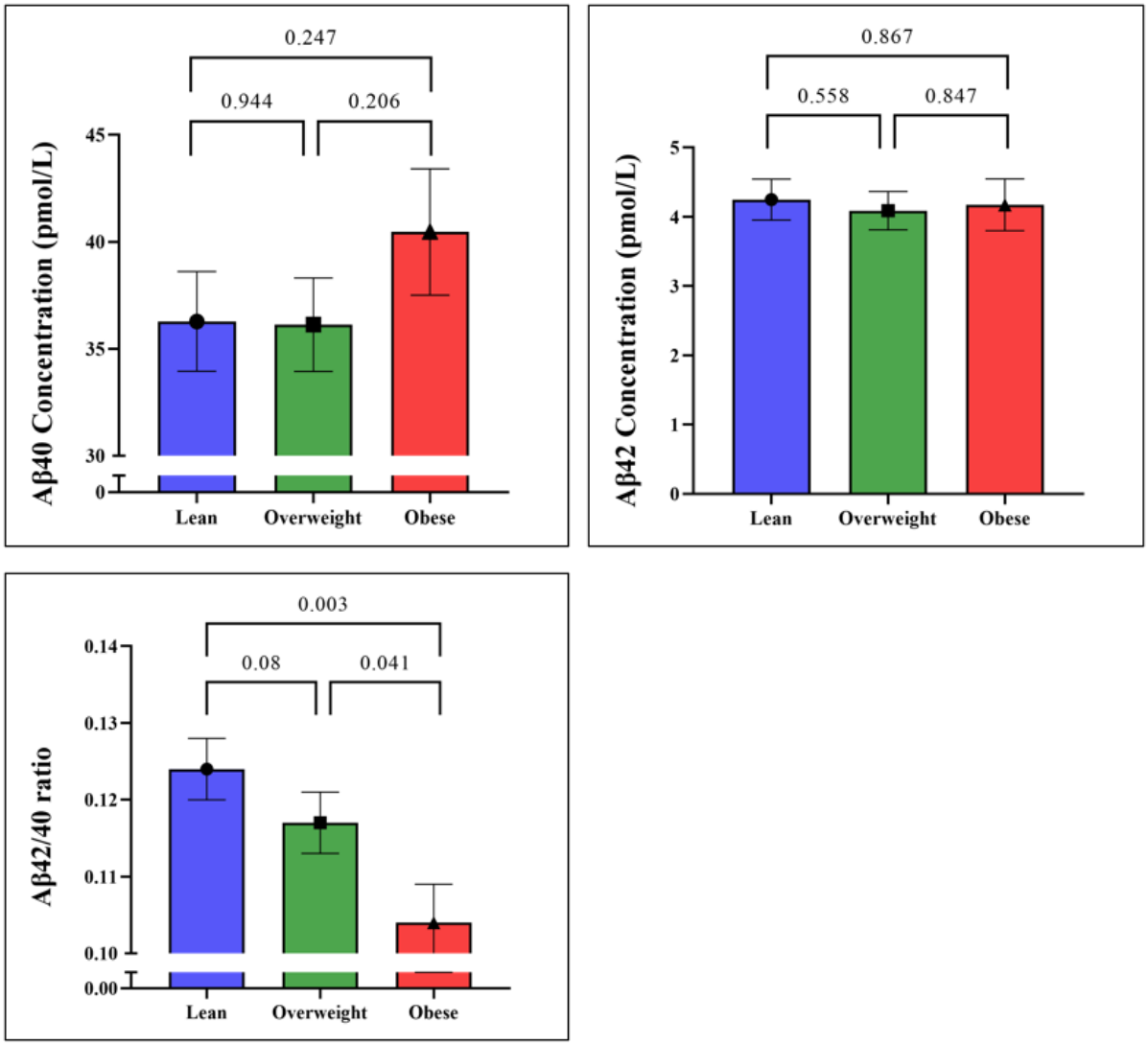

Fig. 3. The bar graphs show adjusted plasma concentrations of A) Aβ40, B) Aβ42, and C) Aβ42/40 ratio in people with lean, overweight, and obese BMIs. All values are shown as mean and standard error of the mean.

To further explore the relationship between BMI and plasma Aβ homeostasis, we tested whether reducing BMI in overweight and obese participants alters plasma concentrations of Aβ. After the 12-week weight loss intervention, participants significantly reduced their BMI by an average of 4.18% (Table 2).

Variable	Baseline	wk-12	Change (%)[a]	*p* value
Age (years) (range)	60.08 ± 5.016 (45-66)	-	-	-
BMI (kg/m^2) (range)	33.14 ± 5.484 (26.33-51.07)	31.76 ± 5.400 (25.23-48.47)	–4.184 ± 2.466 (–9.584-1.672)	<0.0001

Table 2: Age and BMI at baseline and wk-12

All values are presented as mean ± SD with range

[a]Percent change from baseline to 12-week follow-up

Plasma concentrations of Aβ40, Aβ42 and Aβ42/40 ratio for baseline and 12-weeks are shown in Figure 4. Following weight loss, plasma Aβ40 significantly decreased by 6.5% (Fig 4A), whilst plasma Aβ42 and the Aβ42/40 ratio did not show any significant changes (Fig 4B-C).

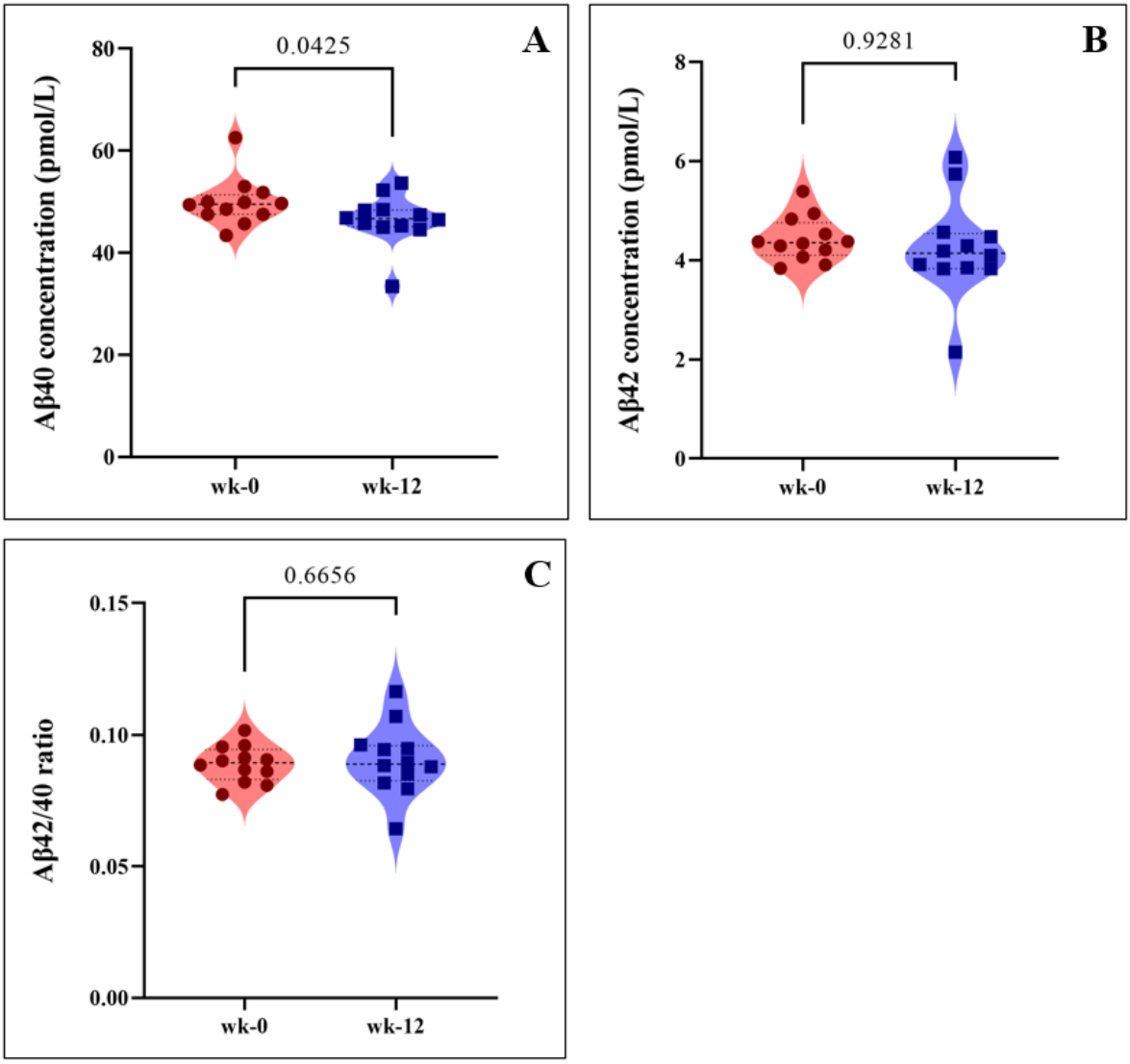

Fig. 4. Violin plot shows the plasma concentrations of A) Aβ40, B) Aβ42, and C) Aβ42/40 in people before and after the calorie-restriction weight-loss program. The median value is indicated by the solid line, and the quartiles are represented by the dashed lines.

We also performed correlation analysis between the change in plasma Aβ and percentage of weight loss (Fig 5). Overall, plasma Aβ40 shows a moderate negative correlation with percentage of weight lost, however this failed to reach statistical significance (Fig 5A). Plasma Aβ42 and Aβ42/40 ratio did not show any significant correlations with weight-loss (Fig 5B-C).

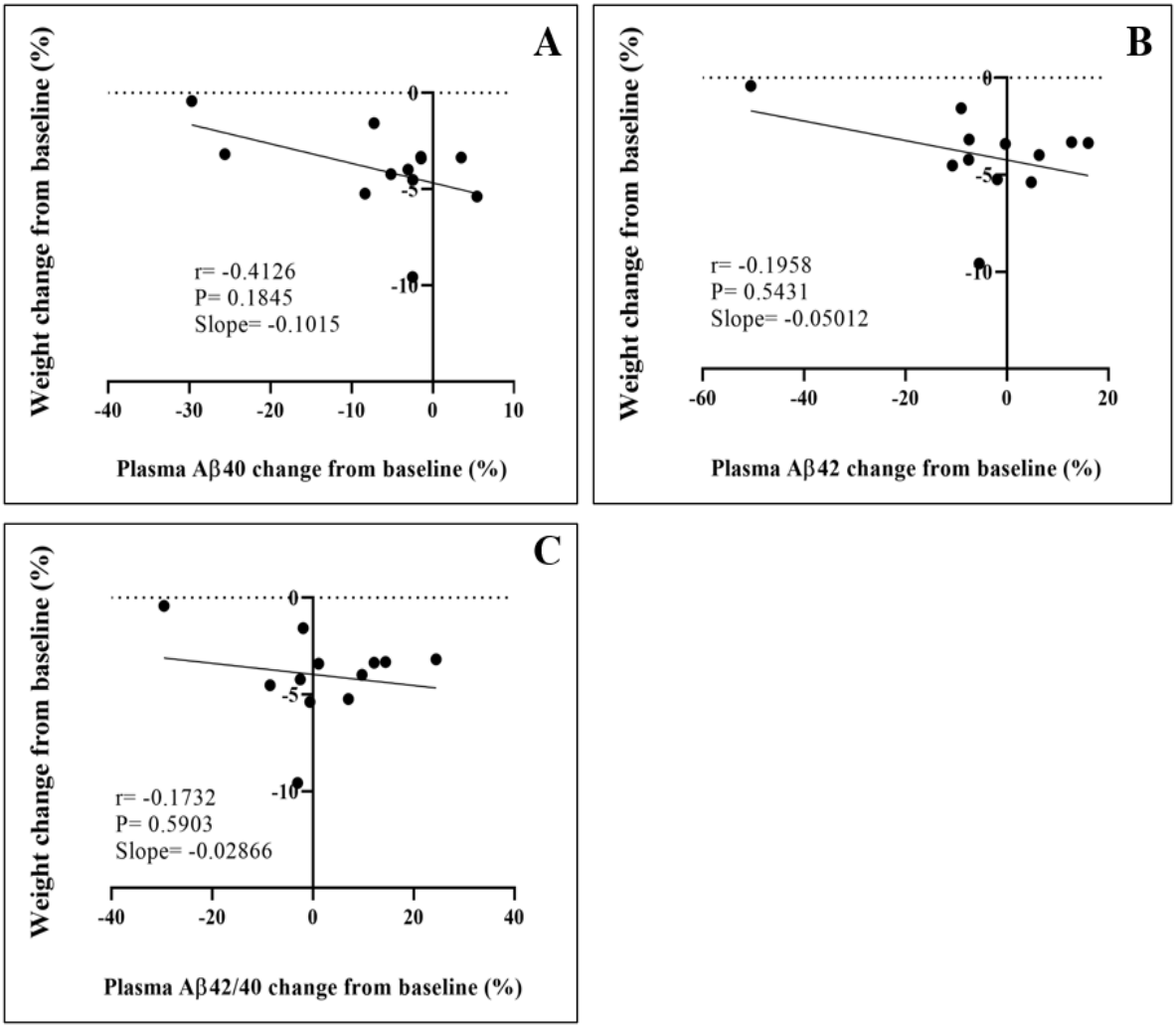

Fig. 5. The scatter plot shows the linear correlations between the percentage of weight loss from baseline and percent change in plasma concentrations of A) Aβ40, B) Aβ42, and C) Aβ42/40 ratio.

DISCUSSION

In the present study, we investigated whether increased risk of AD in obesity is associated with plasma Aβ dyshomeostasis and examined the relationship between BMI and plasma Aβ concentrations of 106 adults.

Here, we report that plasma Aβ40 is significantly elevated in obese participants compared to those in the overweight and lean groups. Consistently, plasma Aβ40 showed significant positive correlation with BMI. In contrast, plasma Aβ42 did not show significant association with BMI. Nonetheless, BMI showed strong negative correlation with Aβ42/40 ratio and indicated significantly lower Aβ42/40

ratio in the obese group compared to the people classed as lean and overweight. The significant association between obese-BMI and plasma Aβ42/40 ratio were persistently observed after adjusting the data to age, age-squared and sex, whilst Aβ40 and Aβ42 did not show any independent significant differences between lean, overweight and obese groups. The low plasma Aβ42/40 ratio observed amongst the obese BMI group coincides with a greater risk of AD, as lower plasma Aβ42/40 ratio is consistently associated with high cerebral amyloid burden, greater cognitive deterioration and increased risk of developing AD [8-15, 20-23]. Therefore, our data collectively suggest that obesity and higher BMI may implicate a higher risk of AD through disturbances in plasma Aβ homeostasis. However, the underlying mechanisms by which obesity increases plasma Aβ40 and decreases in Aβ42/40 ratio are currently unknown.

Aβ precursor protein (AβPP), the precursor molecule for Aβ generation, is reported to be significantly overexpressed in the adipocytes of obese people compared to a lean population [17, 24], indicating greater availability of Aβ biosynthesis in obesity. Additionally, preclinical findings demonstrate that in obesity the activity of β-site AβPP cleaving enzyme-1 (BACE1), the enzyme responsible for the extracellular cleavage of AβPP and the subsequent production of Aβ, is significantly elevated [25-27]. Moreover, pre-clinical studies report that the production and secretion into circulation of Aβ are predominantly regulated through lipid metabolism [28]. In wild-type mice, ingestion of a diet enriched in saturated fats resulted in significant elevation of Aβ synthesis by the small intestinal enterocytes, which increased plasma Aβ concomitant with heightened non-esterified fatty acids [29, 30]. In alignment with these findings, pharmacological lipid-lowering interventions resulted in the significant reduction of plasma Aβ in wild-type mice [31-34]. These data suggest that impaired lipid metabolism and heightened plasma lipids in obesity may elevate circulating plasma Aβ. Taken together, obesity may directly and indirectly contribute to peripheral Aβ dysregulation and lead to a low Aβ42/40 ratio, which may explain the elevated risk of AD amongst obese populations. However, mechanistic studies are required to delineate the complete effect obesity has on Aβ homeostasis and its contribution to the AD pathological cascade.

Considering that obesity may disturb systemic Aβ homeostasis, we explored whether reducing BMI by calorie-restriction induced weight-loss could normalise plasma Aβ homeostasis in overweight and obese people. Following weight-loss, plasma Aβ40 significantly decreased, whilst plasma Aβ42 and Aβ42/40 ratio remained largely unaffected. Moreover, it is well documented that weight-loss decreases plasma triglycerides and normalises lipid profiles [19, 35, 36]. Given that our previously published findings suggest that lipid metabolism significantly regulates Aβ homeostasis, we speculate that reduced abundance of triglycerides may also lead to decreased plasma Aβ40 [19, 29-34]. Furthermore, loss of adipose during weight-loss may also reduce the availability of amyloidogenic material, and thus also contribute to the reduced Aβ40. Taken together, calorie restriction induced weight loss may modulate Aβ through improved lipid metabolism and fat loss. However, the differential effects weight-loss has on Aβ40, Aβ42 and Aβ42/40 ratio highlight differences in their physiological properties, which warrants further exploration. Overall, the complexities of the relationship between weight-loss, lipid metabolism, and Aβ are largely under studied and requires further research to determine the complete effect calorie restriction has on Aβ homeostasis in people with obesity.

We note that there are several limitations in this study, including the use of BMI as an indicator of obesity. BMI does not consider body composition, therefore, in-depth studies which assess muscle mass and adiposity in relation to Aβ would be useful to further explore how obesity influences peripheral Aβ homeostasis. Additionally, our study did not evaluate cognition over the span of the study nor in a long-term setting, consequently, our conclusions which relate to AD development are to be interpreted cautiously. Lastly, the weight loss reported in this study was relatively short-term, in a limited sample size, and only showed a modest reduction in BMI (<4.2%), which may have led to insignificant changes in plasma Aβ42 and Aβ42/40 ratio. A greater weight loss intervention may realise a better outcome. Ultimately, further mechanistic and longitudinal studies are indeed required to substantiate our study findings and interpretations.

In summary, our data shows that people with an obese BMI show a reduced plasma Aβ42/40 ratio which may translate to a heightened risk of developing AD. Importantly, we also demonstrate that the

reduction of BMI may help normalise plasma Aβ40 dyshomeostasis. The findings may help understand the mechanisms whereby obesity increases AD risks and offer potential preventative opportunity through weight-loss. Further studies are needed to explore exact mechanisms by which obesity induce the dysregulation of plasma Aβ homeostasis.

ACKNOWLEDGEMENTS

This study was funded by the National Health and Medical Research Council.

CONFLICTS OF INTEREST

The authors have no conflict of interest to report

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