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ORIGINAL CONTRIBUTIONS

Neuropsychological Functioning in Mid-life Treatment-Seeking Adults with Obesity: a Cross-sectional Study

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Abstract
Objective The aim of this study is to compare cognitive functioning between treatment-seeking individuals with obesity and healthy-weight adults.
Design and Methods Sixty-nine bariatric surgery candidates (BMI > 30 kg/m^2) and 65 healthy-weight control participants (BMI 18.5–25 kg/m^2) completed a neuropsychological battery and a self-report psychosocial questionnaire battery.
Results Hierarchical regression analyses indicated that obesity was predictive of poorer performance in the domains of psychomotor speed ($p = .043$), verbal learning ($p < .001$), verbal memory ($p = .002$), complex attention ($p = .002$), semantic verbal fluency ($p = .009$), working memory ($p = .002$), and concept formation and set-shifting ($p = .003$), independent of education. Obesity remained a significant predictor of performance in each of these domains, except verbal memory, following control for obesity-related comorbidities. Obesity was not predictive of visual construction, visual memory, phonemic verbal fluency or inhibition performance. Individuals with obesity also had significantly poorer decision-making compared to healthy-weight controls.
Conclusions Findings support the contribution of obesity to selective aspects of mid-life cognition after controlling for obesity-related comorbidities, while addressing limitations of previous research including employment of an adequate sample, a healthy-weight control group and stringent exclusion criteria. Further investigation into the functional impact of such deficits, the mechanisms underlying these poorer cognitive outcomes and the impact of weight-loss on cognition is required.

Keywords Obesity · Body mass index · Cognition · Bariatric surgery · Executive function · CVD risk factors

Introduction

Obesity is a leading cause of preventable disease worldwide [1]. Obesity is associated with a range of health conditions including cardiovascular disease (CVD), diabetes, osteoarthritis, various forms of cancer [2] and depression [3]. Recent research has also revealed an association between mid-life obesity and cognitive decline and dementia [4], which could have considerable public health implications in the context of an ageing population and the growing prevalence of obesity. This association between obesity and dementia has prompted consideration of whether mid-life cognitive function is also compromised in adults with obesity. Should cognitive dysfunction be evident in mid-life, prior to age-related cognitive decline, this would provide an opportunity for early detection, prevention and intervention. Emerging findings suggest that obesity may be associated with lowered mid-life cognitive performance in a variety of domains [5], signifying a

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relationship between obesity and cognition prior to any age-related cognitive changes or progression to dementia.

However, existing research examining mid-life obesity-related cognitive deficits has two important limitations. Firstly, few studies have comprehensively assessed a full range of cognitive domains, meaning it is unclear which aspects of cognition may, or may not be, affected in individuals with obesity [6]. Secondly, research has been inconsistent in controlling for obesity-related comorbidities known to impact cognition (e.g. cardiovascular (CVD) risk factors, depression; [6]) despite the heightened prevalence of these conditions in individuals with obesity [7, 8] and their known links to cognitive function [9–12]. Consequently, the domains of cognitive function affected in mid-life obesity, and the contribution of obesity to this relationship following stringent control of confounding variables remains unclear. This study therefore aimed to compare domain-specific cognitive functioning in treatment-seeking individuals with obesity and healthy-weight adults, and to determine whether obesity contributes to cognitive function once the confounding effects of obesity-related comorbidities have been considered.

Method

Study Design

A cross-sectional study design was employed to compare domain-specific cognitive functioning between treatment-seeking individuals with obesity and healthy-weight adults.

Participants

Participants included 69 adults with obesity seeking weight-loss surgery consecutively recruited through a surgical weight-loss clinic in Melbourne, Australia, and 65 healthy-weight adults were recruited using distribution of emails, online advertisements and posters in the general community. Individuals who expressed interest in this study advertisement were given study information and were contacted following completion and return of the consent form.

Both groups were aged between 18 and 65 years (inclusive). Obese participants had a BMI greater than 30 kg/m^2. Current clinical practice guidelines [13] suggest bariatric surgery may be considered for individuals with BMI > 30 kg/m^2 who have serious and poorly controlled comorbidities (i.e. type II diabetes). Healthy-weight participants had a BMI between 18.5–25.9 kg/m^2 [14]. As per best practice in neuropsychological research [15], the obese sample was compared to a healthy-weight control group matched on age and gender demographics that were unable to be matched between groups (i.e. education) were controlled for in all analyses.

Prior to participation, all participants were contacted by telephone to screen for a history of significant developmental or acquired brain injury, psychiatric illness (e.g. schizophrenia, bipolar disorder) and substance abuse history. This interview involved a series of predetermined questions designed to determine history of conditions likely to affect cognitive performance. For example, "Have you ever been diagnosed with any brain-related disorder such as epilepsy, a brain tumour, or multiple sclerosis?" and "Have you ever been diagnosed with a psychiatric disorder such as schizophrenia". Table 1 outlines inclusion and exclusion criteria.

Materials

Health Measurements

Health measurements included height, weight, and blood pressure and blood tests, measuring fasting blood glucose (FBG), triglycerides and HDL-cholesterol (HDL-C).

Questionnaires

All participants completed a battery of questionnaires including items assessing demographic variables (e.g. age, gender, and education), history of sleep apnoea diagnosis and the following self-report measures. Anxiety and depression were measured using the Anxiety and Depression subscales of the

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
18 to 65 years old (inclusive)	Significant developmental or acquired brain injury
BMI > 30 kg/m^2 (obese-weight group)	History of diagnosed severe psychiatric illness
BMI between 18.5–25 kg/m^2 (healthy-weight group)	Major substance abuse history
	Non-fluency in English
	Uncorrected vision or motor problems
	Previous significant learning difficulty
	Medication use likely to impact cognitive performance
	Any form of past bariatric surgery

14-item Hospital Anxiety and Depression Scale (HADS; [16]). The HADS was selected as it omits items common to both illness and anxiety and depression (e.g. fatigue, sleep problems) meaning it can more accurately identify anxious and depressive symptoms in people with physical health issues. A measure of symptoms was selected as the goal was to control for the effect of depressive and anxious symptoms rather than discrete psychiatric diagnoses, where the threshold of symptoms to receive a diagnosis are high. The Fatigue Symptom Inventory (FSI; [17]) was selected to assess current fatigue, "Rate your level of fatigue right now" (item 4). Current fatigue was assessed so that the effect of fatigue on neuropsychological test performance could be controlled for as order of test administration was unable to be randomised.

Neuropsychological Measures

Pen and paper and computerised (Inquisit; [18]) neurocognitive instruments were selected to assess a range of cognitive domains according to a range of predetermined criteria [6] including adequate psychometric properties, sensitivity, absence of ceiling effects, and practical considerations (e.g. cost, logistics, and administration time). A detailed test selection process was undertaken in order to address limitations of previous research [6] including the scarcity of studies to have comprehensively assessed a full range of cognitive domains in this population (aim 1). The test selection process involved consideration of inter-rater reliability, and many tests were computer based meaning inter-rater error is removed.

Psychomotor speed was assessed using the total score of the Symbol Digit Modalities Test (SDMT; [19]).

Verbal learning and memory was measured using the California Verbal Learning Test-Second Edition (CVLT-II; [20]). To avoid ceiling effects, only three recall administrations (rather than five) and one 30-min delayed recall administration were employed. The number of correct words recalled over the three initial presentations, and the number of correct words following delay were used as measures of verbal learning and verbal memory, respectively.

Visual construction and visual memory was measured using the Rey Complex Figure Test (RCFT; [21]) total copy and delay administration scores, respectively, scored using the Meyers and Meyers scoring system [21].

Complex attention was measured using time to complete Part A subtracted from time to complete Part B (to control for basic psychomotor speed) on the Trail Making Test (TMT; [22]).

Phonemic verbal fluency was measured using the total number of words recalled over the three letter trials of the Verbal Fluency Test [23]. Semantic verbal fluency was assessed using the total number of animals named on the Animal Naming Task [23],

Working memory was measured using the overall accuracy of responses on a computerised N-Back Task [24]. Each participant makes two attempts at each *n*-level (i.e. $n = 1$, $n = 2$ or $n = 3$) and accuracy of response was calculated by subtracting incorrect responses from correct response across all conditions.

Decision-making was assessed using a computerised version of the Iowa Gambling Task (IGT; [25]). Scores were calculated in five blocks of 20 cards, where the number of disadvantageous choices (selection from decks A and B) were subtracted from the number of advantageous choices (selection from decks C and D), with higher scores indicating better performance.

Inhibition was measured using the overall accuracy of inhibition responses on a computerised Stop Signal Reaction Time task (SSRT; [26]).

Concept formation and set-shifting was measured using the total number of cards to completion on a computerised Wisconsin Card Sorting Test (WCST; [27]).

Procedures

Prior to data collection, a power calculation was conducted using the GPower statistical software [28] to estimate the sample size required for each group. This calculation was based on an estimated medium effect, powered by an 80% chance of finding an effect, an alpha level of .05, two groups and ten covariates. A medium effect size was selected as the available literature assessing cognitive deficits in mid-life adults with obesity suggested average moderate effect sizes. This power analysis suggested each group would need approximately 65 individuals.

Data was collected between October 2012 and May 2014. The neuropsychological testing was conducted by senior registered trainee psychologists under the supervision of a Clinical Neuropsychologist. Test administration and scoring competence and inter-rater reliability between researchers were established as part of the training process.

Individuals with obesity were recruited as part of a larger psychological study which involved completion of neuropsychological tests (approximately 75 min), followed by other structured psychological interviews (total assessment time approximately 2 h). The healthy-weight group were recruited specifically for this study and their assessment involved health measurements (15 min) and neuropsychological tests (total assessment time approximately 75 min).

Results

Demographics

Groups did not differ significantly in age, $t(120.31) = 1.87$, $p = .06$ (individuals with obesity 43.01 ± 10.18 years; individuals of healthy weight 39.2 ± 13.19 years). Groups did not differ

significantly in gender $\chi^2(1, N = 134) = 0.37$, $p = .55$ (individuals with obesity 74% female; individuals of healthy weight 77% female). As expected, BMI was significantly different between groups, $t(74.65) = 20.46$, $p < .001$ (individuals with obesity 43.06 ± 8.35 kg/m^2; individuals of healthy weight, BMI 22.72 ± 1.73 kg/m^2). The BMI distributions within the group with obesity were as follows: Class I (13%), Class II (33%), and Class III (54%). Healthy-weight controls reported higher education levels, $t(124.50) = -2.04$, $p = .04$, and therefore education was controlled for in all subsequent analyses. Groups differed significantly on anxiety and depression scores $\chi^2(3, N = 134) = 10.93$, $p = .012$ and $\chi^2(2, N = 134) = 18.39$, $p = .000$, respectively. Table 2 summarises participant demographic, health and psychological characteristics.

Preliminary Analysis of Relationships Between Demographic, Health, Psychological and Cognitive Variables

All data analyses were conducted using IBM SPSS Statistics 22. Predictors to be included in the subsequent regression models were determined from between group comparisons (Table 2) and bivariate correlations (Table S1). Significant correlations emerged between all predictors (except HDL-C) and at least one cognitive outcome variable.

Comparison of Neuropsychological Performance Between individuals of Obese and Healthy Weight

To compare cognitive performance between groups of obese and healthy weight in a way consistent with previous studies, a series of hierarchical multiple regression analyses (group as the predictor and education as covariate) were conducted for each neuropsychological outcome measure. Variables were entered in the following steps. Step 1: Education (years of education); Step 2: Group (obese and healthy-weight control).

At Step 1, education (years) predicted cognitive performance in all domains except visual memory, phonemic verbal fluency and inhibition (Table 3). At Step 2, obesity predicted poorer performance in the following domains: psychomotor speed, verbal learning, verbal memory, complex attention, semantic verbal fluency, working memory and concept formation and set-shifting. No significant obesity effect was demonstrated in visual construction, visual memory, phonemic verbal fluency or inhibition.

To assess the contribution of obesity to cognitive performance independent of related comorbidities (aim 2), a further series of hierarchical multiple regression analyses were conducted with variables entered in the following steps. Step 1: Education (years of education); Step 2: Mood and Sleep (Fatigue, sleep apnoea diagnosis, depression, anxiety); Step 3: CVD factors (Systolic

Table 2 Demographic, health, and psychological characteristics of participants

	Individuals of obese weight *N* = 69 *M* (SD)	Individuals of healthy weight *N* = 65 *M* (SD)	*p*
BMI (kg/m^2)	43.06 (8.35)	22.72 (1.73)	$p < .001$*
Class I	13% (*N* = 9)		
Class II	33% (*N* = 23)		
Class III	54% (*N* = 37)		
Age (years)	43.01 (10.18)	39.2 (13.19)	$p = .06$
Gender	Male 26% (18) Female 74% (51)	Male 23% (15) Female 77% (50)	$p = .55$
Education (years)	14.59 (1.70)	15.12 (1.25)	$p = .04$*
English first language	96% (67)	92% (60)	$p = .24$
Anxiety	8.40 (3.68)	6.34 (3.43)	$p = .001$*
Depression	6.53 (3.51)	2.14 (2.35)	$p < .001$*
Fatigue	4.30 (2.05)	3.08 (2.15)	$p = .001$*
Systolic blood pressure (mm Hg)	145.08 (14.01)	118.57 (14.66)	$p < .001$*
Diastolic blood pressure (mm Hg)	89.23 (11.46)	69.68 (9.62)	$p < .001$*
Fasting blood glucose (mmol/L)	5.82 (1.50)	4.90 (.39)	$p < .001$*
Triglycerides (mmol/L)	1.55 (0.72)	0.81(0.27)	$p < .001$*
HDL-Cholesterol (mmol/L)	1.45 (0.37)	1.65 (0.39)	$p < .001$*
History of sleep apnoea	24% (17)	1.5% (1)	$p < .001$*

t tests conducted for BMI, age, education, depression, anxiety, fatigue and blood variables. Chi-square comparisons conducted for gender, English first language and sleep apnoea diagnosis

*$p < .05$

Table 3 Comparison of neuropsychological performance in adults of obese and healthy weight (controlling for education)

	Step 1		Step 2		
Predictor	Education		Group		Significant individual predictors (Step 2)
Cognitive domain	R^2	F change (df)	R^2 change	F change (df)	
Psychomotor speed	0.15***	(1, 132) = 23.08	0.03*	(1, 131) = 4.16	Education ($p < .001$) and group ($p = 0.043$)
Verbal learning	0.10***	(1, 132) = 14.50	0.09***	(1, 131) = 14.07	Education ($p < .001$) and group ($p < .001$)
Verbal memory	0.13***	(1, 132) = 20.41	0.06**	(1, 131) = 9.63	Education ($p < .001$) and group ($p = 0.002$)
Visual construction	0.09**	(1, 132) = 12.37	0.01	(1, 131) = 0.75	Education ($p = .001$)
Visual memory	0.02	(1, 132) = 2.36	0.00	(1, 131) = 0.21	None
Complex attention	0.07**	(1, 132) = 10.14	0.07**	(1, 131) = 10.48	Education ($p = .002$) and group ($p = .002$)
Phonemic verbal fluency	0.02	(1, 132) = 2.47	0.02	(1, 131) = 3.27	None
Semantic verbal fluency	0.08**	(1, 132) = 11.97	0.05**	(1, 131) = 6.97	Education ($p = .001$) and group ($p = .009$)
Working memory	0.05*	(1, 132) = 6.37	0.06**	(1, 131) = 8.93	Education ($p = .003$) and group ($p = .002$)
Inhibition	0.00	(1, 132) = 0.41	0.00	(1, 131) = 0.37	None
Concept formation and set-shifting	0.05*	(1, 132) = 6.37	0.06**	(1, 131) = 8.93	Education ($p = .013$) and group ($p = .003$)

*$p < .05$, **$p < .01$, ***$p < .001$

blood pressure (SBP), triglycerides, HDL-C, FBG); Step 4: Group (obese and healthy-weight control).

At Step 1, education predicted cognitive performance in all domains except visual memory, phonemic verbal fluency and inhibition (Table 4). At Step 2, fatigue, anxiety, depression and sleep apnoea significantly predicted performance on verbal learning, verbal memory and concept formation and set-shifting. At Step 3, the metabolic variables only significantly predicted performance on visual memory and concept formation and set-shifting. At Step 4, obesity predicted poorer psychomotor speed, verbal learning, complex attention, semantic verbal fluency, working memory and concept formation and set-shifting.

Decision-Making Performance

IGT performance cannot be represented in a single score like other tests as decision-making is assessed on deck selection across the duration of the task. Therefore, decision-making performance was assessed in a separate analysis using a two (group, between subjects) by five (blocks, within subjects) repeated measures analysis of covariance (ANCOVA), controlling for education. No group × block interaction was demonstrated, $F(3.87, 506.35) = 1.69$, $p = .15$). A significant main effect was evident for group ($F(1131) = 5.55$, $p = 02$), but not blocks ($F(3.87, 506.35) = 1.19$, $p = .31$), see Fig. 1.

Discussion

Summary of Findings

This study aimed to compare domain-specific cognitive performances between individuals of obese versus healthy weight, and to determine the contribution of obesity to cognitive performance after controlling for obesity-related comorbidities. Compared to healthy-weight counterparts, individuals with obesity demonstrated reduced cognitive performance in psychomotor speed, verbal learning, verbal memory, complex attention, semantic verbal fluency, working memory, decision-making and concept formation and set-shifting. These findings remained significant after controlling for obesity-related comorbidities for all cognitive outcomes, except verbal memory. Obesity did not have a significant association with visual construction, visual memory, phonemic verbal fluency, or inhibition before or after controlling for sleep, mood and CVD variables.

Overall these findings reflect a pattern of impairment in attention, learning and executive dysfunction that is largely consistent with previous literature [5, 6]. The pattern of attention, learning and executive impairment implies specific brain region dysfunction, primarily in the prefrontal cortex, medial temporal and subcortical regions [29–33]. These findings are aligned with emerging neurological research indicating that these regions may be affected in individuals with obesity [34–37], including findings that elevated BMI is associated with mid-life decreases in prefrontal cortex function [35, 36]. The current findings are aligned with this emerging neuroimaging research, suggesting that obesity may impact on specific areas of brain function resulting in selective mid-life cognitive dysfunction prior to any age-related cognitive decline.

Following control for obesity-related comorbidities, all domains (except verbal memory) retained a significant association with obesity. This means that not only does obesity contribute to cognitive impairment in a range of domains, but that the pattern of this impairment remains largely unchanged after

Table 4 Comparison of neuropsychological performance in individuals of obese and healthy weight, independent of obesity-related comorbidities (education, sleep and mood, and CVD risk factors)

	Step 1		Step 2		Step 3		Step 4		
Predictors	Education		Sleep and mood: fatigue, depression, anxiety, sleep apnoea		CVD risk factors: SBP, FBG, Triglycerides, HDL-C		Group		Significant individual predictors (Step 2)
Cognitive domain	R^2	*F* change (df)	R^2 change	*F* change (df)	R^2 change	*F* change (df)	R^2 change	*F* change (df)	
Psychomotor speed	0.15***	(1, 132) = 23.08	0.88	(4, 128) = -0.88	0.06	(4, 124) = -2.26	0.03*	(1, 123) = -4.13	Education ($p < .001$), FBG ($p = .016$) and group ($p = .044$)
Verbal learning	0.10***	(1, 132) = 14.50	0.09**	(4, 128) = -3.68	0.02	(4, 124) = -0.87	0.04*	(1, 123) = -6.66	Education ($p = .001$), anxiety ($p = .018$) and group ($p = .011$)
Verbal memory	0.13***	(1, 132) = 20.41	0.10**	(4, 128) = -4.05	0.01	(4, 124) = -0.59	0.02	(1, 123) = -2.74	Education ($p < .001$)
Visual construction	0.09**	(1, 132) = 12.37	0.02	(4, 128) = -0.67	0.06	(4, 124) = -2.13	0.01	(1, 123) = -1.75	Education ($p = .001$) and FBG ($p = .009$)
Visual memory	0.02	(1, 132) = 2.36	0.02	(4, 128) = -0.80	0.08*	(4, 124) = -2.88	0.00	(1, 123) = -0.07	FBG ($p = .019$)
Complex attention	0.07**	(1, 132) = 10.14	0.04	(4, 128) = -1.47	0.03	(4, 124) = -1.08	0.05**	(1, 123) = -7.22	Education ($p = .008$) and group ($p = .008$)
Phonemic verbal fluency	0.02	(1, 132) = 2.47	0.02	(4, 128) = -0.63	0.01	(4, 124) = -0.15	0.02	(1, 123) = -3.15	None
Semantic verbal fluency	0.08**	(1, 132) = 11.97	0.04	(4, 128) = -1.25	0.04	(4, 124) = -1.43	0.03*	(1, 123) = -4.59	Education ($p = .010$), FBG ($p = .034$ and group ($p = .034$)
Working memory	0.07**	(1, 132) = 9.18	0.05	(4, 128) = -1.91	0.03	(4, 124) = -1.25	0.04*	(1, 123) = -6.70	Education ($p = .008$), fatigue ($p = .047$) and group ($p = .011$)
Inhibition	0.00	(1, 132) = 0.41	0.04	(4, 128) = -1.31	0.01	(4, 124) = -0.43	0.00	(1, 123) = -0.00	None
Concept formation and set-shifting	0.05*	(1, 132) = 6.37	0.10**	(4, 128) = -3.85	0.07*	(4, 124) = -2.85	0.04*	(1, 123) = -5.88	Education ($p = .011$), fatigue ($p = .004$), HDL-C ($p = .003$) and group ($p = .017$)

*$p < .05$, **$p < .01$, ***$p < .001$

controlling for important cardiovascular comorbidities. This suggests that the obesity-cognition relationship cannot be explained by psychological and cardiovascular factors alone, and as such mechanisms specific to obesity may, in part,

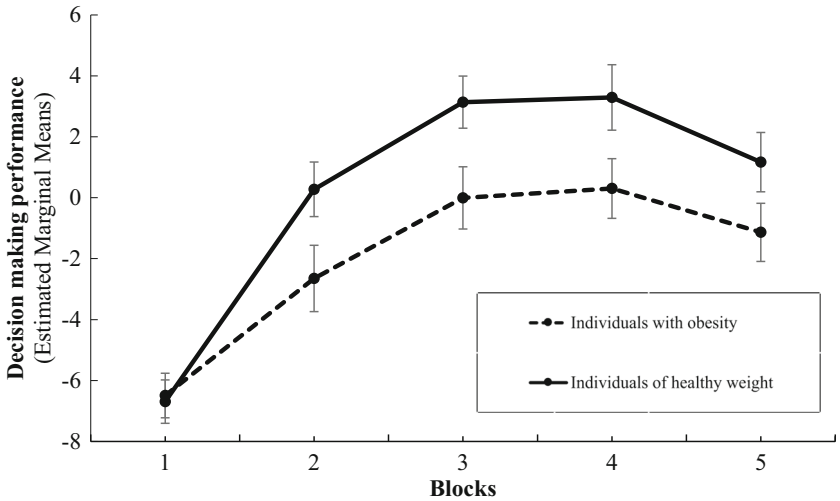

Fig. 1 Difference scores ([decks C + D] − [decks A + B]) across the five blocks of the Iowa Gambling Task plotted separately for individuals of obese and healthy weight, controlling for education

underlie this relationship. A range of mechanisms including metabolic and endocrine abnormalities (e.g. inflammation [38, 39], cortisol [40–43]), and structural brain changes (including grey matter atrophy and white matter changes [42–44]), have already been proposed within existing literature. Further research in animal models will allow examination of the specific structural, metabolic, and endocrine changes underlying the cognitive effects of obesity; and human studies assessing mechanisms and cognition simultaneously via the use of high-resolution imaging techniques including fMRI to understand the complex interactions of variables underlying obesity-related cognitive impairment.

Functional research will be particularly important particularly as most available research to date, including the present study, has only demonstrated cognitive deficits using psychometric tests [5, 6]. Little research has focussed on whether these mid-life cognitive impairments impact on general function (e.g. social and occupational functioning) or more specifically weight-related behaviours (e.g. making decisions or adhering to important health information [45, 46]). The potential for these deficits to impact function is concerning given many other comorbidities of obesity (e.g. depression, diabetes) already have considerable functional implications for individuals with obesity, and further impairments may compound this burden. Understanding of the functional impact of obesity-related cognitive dysfunction is a significant gap in the available literature that will need to be addressed by future research.

Finally, the presence of cognitive deficits in mid-life demonstrated in this study and a growing body of literature, in combination with research indicating a relationship between mid-life obesity and cognitive decline [4], suggests such deficits may be the precursor to further cognitive decline over time. Further longitudinal research however is required to explore this supposition. The present findings that obesity is associated with cognitive dysfunction once controlling for related comorbidities suggests that weight-loss could have the potential to improve cognitive outcomes, both directly via its impact on weight, and indirectly via its impact on obesity-related comorbidities. While there are limited investigations of this to date, emerging research suggests that weight-loss may result in improved mid-life cognition [47–49]. As with these studies, bariatric surgery interventions will continue to provide a key means of investigating this relationship, given the capacity for these interventions to achieve significant and sustained weight-loss. Longitudinal evaluation of whether mid-life weight-loss can attenuate cognitive effects of obesity will be crucial, particularly given reducing late-life dementia risk via mid-life weight-loss could have considerable individual (e.g. improving quality of life) and public health (e.g. reducing economic burden) implications in the context of an ageing population and the rising levels of obesity and dementia worldwide.

Strengths and Limitations

An important contribution of the current study is demonstrating that cognitive deficits which have been demonstrated in bariatric surgery patients in other countries also exist within an Australian sample. This study also addressed several limitations of previous research by including an adequate sample size, a well-matched healthy-weight control group and appropriate exclusion criteria. Measures were carefully selected to be reliable, valid and sensitive to subtle deficits, and this is one of few studies to have delineated the contributions of obesity-related comorbidities to cognitive dysfunction from the effect of obesity [6]. However, while the present study builds on previous findings by providing evidence for an effect for obesity on cognitive function by more comprehensively controlling for potential confounding variables of the obesity-cognition relationship, the present analyses do not allow for conclusions to be drawn regarding the independent contribution of obesity to cognitive function. Future research should further explore this important question.

Additional limitations of the sample and analyses must also be acknowledged. Education differed significantly between groups and was thus controlled for in all analyses. Furthermore, the current sample was predominantly female, which is representative of a bariatric surgery seeking sample (approximately 80% female; [50], but is not representative of populations with obesity more generally. Future research should investigate whether the present findings are representative of men seeking bariatric surgery. Additionally, as treatment-seeking samples differ from the general population of individuals with obesity (e.g. higher prevalence of comorbidities including diabetes, depression), these findings may not generalise to nontreatment-seeking samples. It is also acknowledged that binge eating disorder (BED) and other related disorders (e.g. night eating syndrome (NES)) have not been considered as potential confounders of cognitive performance in this clinical sample. While evidence remains limited for a relationship between BED and cognitive dysfunction in obese individuals [51], it is possible that NES, a condition frequently demonstrated in obese individuals [52, 53]), could impact cognitive function at least due to negative sleep impacts. Finally, it should be noted that this study did not control for multiple comparisons (i.e. type I error). This was justified given the exploratory aims and that each of the cognitive outcome measures was considered a unique construct. The cross-sectional nature of this research also meant that the directional relationship between obesity and cognitive function could not be assessed.

Conclusions

Overall, these findings confirm that cognitive difficulties are occurring in mid-life treatment-seeking individuals earlier than potentially first thought, and highlights that the brain is vulnerable to obesity itself, not just its related comorbidities. The consistent evidence of objective cognitive impairment in mid-life raises significant concerns for the vulnerability of the brain to mid-life obesity, and the long-term implications of obesity for cognitive decline and dementia development. The contribution of both obesity and its related comorbidities to cognitive performance underscores the importance of future research investigating the underlying mechanisms and real-world impact of such deficits. The relationship between weight-loss and cognitive function also warrants attention. The identified cognitive domains associated with dysfunction in this population also provide potential targets for future studies investigating the amelioration of cognitive difficulties with weight-loss. Treatment-seeking samples will continue to provide a unique opportunity for such research which will be imperative to enabling the development of both preventative and treatment interventions targeting obesity and obesity-related cognitive impairment. This will be particularly important given the concerning associations between obesity and dementia risk in the context of the growing prevalence of obesity and an ageing population both in Australia and worldwide.

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Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Ethical Statement All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent Statement Informed consent was obtained from all individual participants included in the study.

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