



Obesity and episodic memory function

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Abstract

Obesity-related lifestyle factors, such as physical activity behavior and dietary intake, have been shown to be associated with episodic memory function. From animal work, there is considerable biological plausibility linking obesity with worse memory function. There are no published systematic reviews evaluating the effects of obesity on episodic memory function among humans, and examining whether physical activity and diet influences this obesity–memory link. Thus, the purpose of this systematic review was to evaluate the totality of research examining whether obesity is associated with episodic memory function, and whether physical activity and dietary behavior confounds this relationship. A review approach was employed, using PubMed, PsychInfo, and Sports Discus databases. Fourteen studies met our criteria. Among these 14 reviewed studies, eight were cross-sectional, four were prospective, and two employed a randomized controlled experimental design. Twelve of the 14 studies did not take into consideration dietary behavior in their analysis, and similarly, nine of the 14 studies did not take into consideration participant physical activity behavior. Among the 14 studies, ten found an inverse association of weight status on memory function, but for one of these studies, this association was attenuated after controlling for physical activity. Among the 14 evaluated studies, four did not find a direct effect of weight status on memory. Among the four null studies, one, however, found an indirect effect of BMI on episodic memory and another found a moderation effect of BMI and age on memory function. It appears that obesity may be associated with worse memory function, with the underlying mechanisms discussed herein. At this point, it is uncertain whether adiposity, itself, is influencing memory changes, or rather, whether adiposity-related lifestyle behaviors (e.g., physical inactivity and diet) are driving the obesity–memory relationship.

Keywords Adiposity · BMI · Cognition · Diet · Exercise · Physical activity

Introduction

Obesity has been identified as a risk factor for Alzheimer’s disease [1–3]. Similarly, obesity-related behaviors, such as diet and physical activity have also been shown to influence Alzheimer’s disease risk [4, 5]. There are mixed findings regarding the relationship between obesity and episodic memory function [6], or memories/representations of specific personal experiences that occur in a temporal or spatial context. In some studies [7, 8], but not all [9, 10], obesity is associated with worse episodic memory, as well as other memory parameters, such as visual working memory tasks

[11]. In addition to obesity phenotype, obesity genotype has also been linked with reduced memory, specifically those with at least one copy of the obesity risk-conferring A allele (FTO-AC/AA) [12]. Further, obesity-induced dysregulation of the Sirtuin 1 (Sirt1) gene is also linked with memory deficits [13].

Recently, Cheke et al. [14, 15] developed a what-where-when (WWW) paradigm (Treasure Hunt Task) that comprehensively evaluates episodic memory. This task evaluates not only object-related recollection of the task but also temporal and spatial aspects of memory, both of which are common in everyday life. In this study [14], both obesity and insulin resistance were associated with reduced neural activity in key areas of the brain that subserve episodic memory function (e.g., hippocampus, angular gyrus, and dorsolateral prefrontal cortex).

As detailed below, there are several mechanisms through which obesity may detrimentally influence episodic memory performance, of which may include morphological brain

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changes, insulin resistance, neuroinflammation, triglycerides, circulating levels of glucocorticoids, and cerebral metabolite concentrations (Fig. 1) [16]. Notably, the majority of these mechanistic insights come from preclinical (animal) studies, and such, should be interpreted accordingly.

Morphological brain changes

Related to morphological brain changes, Willette and Kapogiannis [17] demonstrated in a review paper that 14 out of 22 studies reported an inverse association between adiposity and temporal lobe volume, with 11 out of 28 studies reporting an inverse association between adiposity and hippocampal volume.

Insulin resistance

Obesity-related insulin resistance has been found to mediate the relationship between worse memory performance and greater reduction in grey matter volume over a 4-year period [18]. Similarly, insulin sensitivity has been shown to mediate the relationship between BMI and working memory-related brain activation [19]. Indeed, Benedict et al. [20–22] demonstrated that an 8-week intranasal insulin administration may improve episodic memory in young healthy adults. Insulin may also influence memory performance via its ability to stimulate neuronal glucose uptake [23], modulate expression of NMDA receptors [24] in the cell membrane [25], and influence levels of acetylcholine and norepinephrine [26, 27], both of which play important roles in memory function [28, 29]. Acetylcholine may enhance memory encoding via its role in increasing theta rhythm oscillations [30], which is an optimal time for memory encoding [31]. Norepinephrine may alter information processing via β_1 receptors to promote

memory retrieval [29]. Regarding NMDA receptors, insulin has been shown to increase the number of active NMDA channels (via new channel molecules to the cell surface by regulated exocytosis; e.g., insulin acts via insulin receptor tyrosine kinase to initiate a signaling cascade involving PI3K, which may induce receptor trafficking and targeting, thereby increasing NMDA density at the synapse) and increase NMDA channel opening [25].

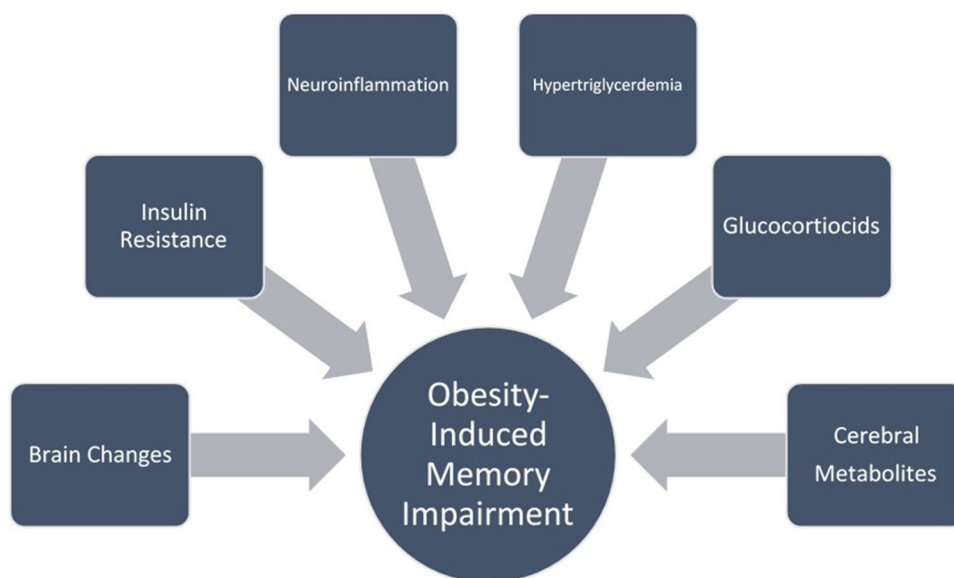
Neuroinflammation

Regarding neuroinflammation (inflammation of nervous tissue) [32], research demonstrates that neuroinflammation is associated with impaired episodic memory [33, 34]. Pro-inflammatory cytokines, such as IL-1, may play a key role in influencing memory-related mechanisms, including long-term potentiation [33]. In situ hybridization studies [35] demonstrate IL-1 receptors are located in the hippocampus, with other work demonstrating that exogenously applied IL-1 can inhibit calcium influx [36], PKA [36], and release of acetylcholine [37] and glutamate [38, 39] in the hippocampus.

Triglycerides

Obesity-related hypertriglyceridemia may also impair episodic memory function [40]. Elevated triglycerides may impair long-term potentiation by blocking NMDA receptor activation [40] and glutamate release [41]. Additionally, hypertriglyceridemia impairs leptin's ability to cross the blood–brain barrier [42], which may have downstream effects on memory, as leptin plays an important role in episodic memory [43]. Specifically, leptin may facilitate the induction of long-term potentiation by enhancing NMDA

Fig. 1 Schematic of potential obesity-related mechanisms subserving episodic memory impairment



receptor-mediated transmission [43], specifically NMDA receptor-mediated Ca^{2+} influx [43]. Importantly, however, high levels of leptin could be counterproductive as high levels of leptin are associated with many inflammatory conditions [44].

Glucocorticoids

Elevated glucocorticoids (or cortisol, in humans), common in obesity [45–47], is another mechanism through which obesity may influence episodic memory function [48]. The hippocampus contains the largest density of corticosterone receptors, which is the principle site for glucocorticoids [49, 50]. Elevated levels of glucocorticoids have been shown to be associated with reduced brain activity in the hippocampus [51]. Additionally, glucocorticoid receptor antagonist administration (RU486) attenuated memory decline in a mouse model of Alzheimer's disease [52]. Exposure to acute uncontrollable stress has been shown to have similar detrimental effects on long-term potentiation when compared to administration of NMDA receptor antagonism drugs [53]. The mechanism of this glucocorticoid effect on long-term potentiation, occurring within the CA1 hippocampal field [54] and dentate gyrus granule cell layer [55], is likely multifold. High levels of acute glucocorticoids are believed to produce an increase of synaptic GABA levels [55], which may have a direct inhibitory effect on long-term potentiation [56, 57]. Chronic elevations of glucocorticoids are suggested to induce atrophy of the size and shape neuronal dendrites [58]. Further, obesity is associated with increased mineralocorticoid receptor (MR) activity [59], which is widely expressed in the hippocampus [60]. In animal studies [61], as well as human studies [62], MR blockage improves hippocampal learning in obesity, and may do so via regulation of hippocampal neuronal activity and associated learning [61, 63].

Cerebral metabolites

Cerebral metabolite concentrations have also been implicated in the obesity–memory relationship. Gonzales et al. [64] demonstrated that elevated BMI was associated with worse memory performance through altered cerebral metabolite concentrations, including creatine (Cr), a marker of membrane breakdown and turnover, and myoinositol (mI), a marker of energy metabolism, osmotic regulator and indicator of gliosis. In the brain, mI serves as an organic osmolyte that helps to protect cells from damage by shrinkage or swelling because of water diffusion changes [65]. Specifically, higher BMI was associated with elevations in mI/Cr, which in turn, was associated with worse memory performance [64], implicating hypertonicity and neuroinflammation as mechanisms underlying

the obesity–memory relationship. These findings are supported by neuroimaging work demonstrating that increased body weight is associated with elevated serum neuron-specific enolase (NSE) concentrations [66], which is a marker of structural neuronal damage [67, 68].

In addition to the aforementioned plausible mechanisms through which obesity (specifically, adiposity) may influence episodic memory function, other work demonstrates that obesity-related diets, such as the “Western diet” (high in saturated fats and simple sugars), has been shown to be associated with deficits in learning and memory [5, 69, 70]. Further, some work suggests that such memory impairments are diet-induced, as opposed to be driven by adiposity changes [71]. For example, recent work demonstrates that memory deficits are observable after as little as 3 days of Western diet consumption [72]. Diet-induced obesity has been shown to decrease dopaminergic signaling [73], which may impair memory as dopamine appears to play an important role in memory function [74]. Similar to glutamate through NMDA and non-NMDA receptors, research demonstrates that dopamine receptor-mediated signals (e.g., via D1 and D2 receptors) are important in the production of long-lasting maintenance of long-term potentiation [75, 76]. For example, dopamine regulation of long-term potentiation may occur via the D1/cAMP/PKA pathway, where the D1 receptor coupled to adenylate cyclase (AC) increases AC activity [74]. This leads to the formation of cAMP that activates PKA, which in turn can phosphorylate transcription factors (e.g., CREB) as well as phosphorylate both AMPA and NMDA receptors [74]. In addition to diet, other obesity-related behaviors, namely physical activity, may play a role in subserving memory function. Details of the potential effects of physical activity on episodic memory function have been thoroughly discussed elsewhere [77]. In brief, physical activity may directly influence cellular mechanisms of episodic memory function via alterations in neuronal excitability and changes in key proteins involved in memory function (e.g., brain-derived neurotrophic factor).

The purpose of this systematic review was to evaluate the totality of research examining the extent to which, indeed, obesity is associated with episodic memory function among an adult population. Additionally, we focus on whether the extracted studies evaluated the extent to which adiposity or obesity-related diets contributed to the relationship between obesity and episodic memory function. Lastly, in the extracted articles, we also evaluate the extent to which physical activity was taken into consideration, as physical activity is closely linked to obesity [78], diet [79, 80], and memory function [81]. Evaluated within the context of the obesity paradox, previous work indicates that physical activity, regardless of weight status, is associated with better memory-related cognitive task performance [82].

To our knowledge, no such comprehensive review exists. Thus, this review will provide an overview of the relationship between obesity and episodic memory, its underlying mechanisms, and whether the current body of literature on this topic has carefully taken into consideration the effects of physical activity and dietary behavior on the obesity–memory link. To our knowledge, there is no published review specifically evaluating these three parameters. We hypothesize that, based on the plausible aforementioned mechanisms, the majority of work on this topic will demonstrate an inverse association between obesity and episodic memory function.

Methods

Studies were identified using electronic databases, including PubMed, PsychInfo, Sports Discus, and Google Scholar. We employed the computerized searches on December 6, 2017, identifying articles published prior to this date (no restriction was placed on how far back the study was published). The search terms included obesity, overweight, body mass index, waist circumference, memory, and episodic memory. To be eligible for inclusion in this systematic review, studies had to be published in English, employ a cross-sectional, prospective, or experimental design, and be conducted among human adults (18+ years). The independent variable had to be an obesity metric (e.g., BMI), with the outcome variable either being the performance on an episodic memory task or measured neural activity during a memory task or in a memory-related neural structure. Notably, studies that employed an overall cognitive function assessment that included memory as part of this global score were not included (e.g., examples include [83, 84]). Outside these criteria, no specific exclusionary criteria were applied. Both authors performed the computerized searches and confirmed agreement with the identified studies, which included 14 extracted studies.

Study quality assessment

Risk of bias/study quality for all studies was assessed using a checklist developed specifically for this study. This tool was based on the Cochrane Collaboration's instrument for assessing risk of bias. This tool included four items with a yes (1) or no (0) response option. These items included:

Item 1: Was a criterion measure of obesity (i.e., not BMI) used? We recognize that there is not universal agreement on a criterion measure of obesity. A measure, such as DXA or waist circumference, in this study, was considered to be a more criterion measure than BMI.

Item 2: Were relevant covariates (i.e., both diet and exercise) included and evaluated in the analysis?

Item 3: Was a prospective or intervention design used?

Item 4: Were statistically appropriate/acceptable methods of data analysis used?

Results

Table 1 displays the extraction table for the 14 evaluated articles. Among the 14 reviewed studies, 8 were cross-sectional, 4 were prospective, and 2 employed a randomized controlled experimental design. In most of the studies, weight status was based on BMI. Episodic memory function was assessed via a word- or sentence-based learning task for 11 of the studies; one study employed fMRI technology, and two studies comprehensively assessed episodic memory via the what-where-when task.

Twelve of the 14 studies did not take into consideration dietary behavior in their analysis, and similarly, nine of the 14 studies did not take into consideration participant physical activity behavior. With regard to the study quality assessment (Table 2), and out of a max score of 4, 43% (6/14) had a quality score of 1, 43% (6/14) had a score of 2, and 7% (1/14) had a score of 3, and 7% (1/14) had a score of 4. Thus, the majority of studies demonstrated evidence of bias.

Among the 14 studies, ten found an inverse association of weight status on memory function, but for one of these studies, this association was attenuated after controlling for physical activity. Among the 14 evaluated studies, four did not find a direct effect of weight status on memory. Among the four null studies, one, however, found an indirect of BMI on episodic memory and another found a moderation effect of BMI and age on memory function.

Discussion

The purpose of this study was to evaluate human-based studies examining the association between weight status and episodic memory function. The major findings of this review are as follows. First, relatively few published studies have examined the association of weight status on episodic memory among humans. Second, most of these studies demonstrated a detrimental association between weight status and episodic memory, which is biologically plausible, as discussed in the Introduction section. Third, most of the studies used BMI as the weight status metric; it would be worthwhile to examine other related metrics to see if body composition, or the distribution of body fat, differentially influences memory function. Fourth, very few of the studies took participant dietary or physical activity behavior into account when considering the

Table 1 Data extraction table for the evaluated studies

Authors	Study design	Population	Obesity variable	Memory assessment	Assessment of diet	Assessment Results of exercise
Conforto and Gershman (1985) [9]	Cross-sectional	30 Obese and 30 non-obese participants	BMI	Word list recall of food and non-food words	No	No
Cournot et al. (2006) [7]	Prospective	1660 Middle-aged men and 1576 middle-aged women	BMI	Word list learning	No	Yes
Gunstad et al. (2006) [8]	Cross-sectional	486 Participants, age range, 21–82 years	BMI	Word list learning	No	No
Dore et al. (2008) [85]	Cross-sectional	917 stroke- and dementia-free adults; mean age = 62 years	Waist circumference, waist/hip ratio	Verbal memory	No	Yes
Nilsson and Nilsson (2009) [10]	Cross-sectional	Four samples from the Betula study were evaluated	BMI and waist/hip ratio	Sentence learning	Yes, but not factored in the analysis	No
Smith et al. (2010) [89]	Experimental	124 Overweight adults with high blood pressure; mean age = 52 years	BMI and DXA	Verbal paired associates	Yes	Yes
Gunstad et al. (2011) [86]	Prospective	150 Adults (109 bariatric surgery patients and 41 obese controls)	BMI	Verbal list learning task; digit span forward	No	No

Table 1 (continued)

Authors	Study design	Population	Obesity variable	Memory assessment	Assessment of diet	Assessment Results of exercise
Gonzales et al. (2012) [64]	Cross-sectional	55 Adults, aged 40–60 years	BMI	CVLT-II; RCF recall	No	BMI was not directly associated with memory, however, there was an indirect association between BMI and memory via ml/Cr (myo-inositol/creatinine)
Katz et al. (2012) [97]	Cross-sectional	138 Women with systemic lupus erythematosus; mean age = 48 years	BMI, DXA, waist circumference	CVLT-II; rey complex figure test copy trial	No	Obesity was not associated with memory function
Miller et al. (2013) [87]	Prospective	137 Adults (95 bariatric surgery patients and 42 obese controls)	BMI	Verbal list learning task; digit span forward	No	A significant group x time interaction effect was observed, noting that bariatric surgery patients improved on all indices of memory function 12 months post-operatively
Alosco et al. (2014) [88]	Prospective	86 Adults (63 bariatric surgery patients and 23 obese controls)	BMI	Verbal list learning task; digit span forward	No	A significant group x time interaction effect was observed, noting that, relative to obese controls, bariatric surgery patients showed improvements in memory from baseline to 12 weeks and 24 months post-operatively

Table 1 (continued)

Authors	Study design	Population	Obesity variable	Memory assessment	Assessment of diet	Assessment Results of exercise
Boraxbekk et al. (2015) [98]	Experimental	20 Overweight post-menopausal women ($M_{age} = 61$ years)	BMI	fMRI assessment of a face-name paradigm to assess brain responses related to episodic memory.	Yes; randomized into a modified Paleolithic-type diet (PD) or a diet per Nordic Nutrition Recommendations (NNR)	Both diets reduced weight after the 6-month follow-up period. Memory performance improved after the 6-month period, with no differences between the diet groups. Brain activity increased in the hippocampus, prefrontal cortex and temporal gyri, without differences between diets. Neither of the groups significantly changed their physical activity levels across the two assessment periods
Cheke et al. (2016) [99]	Cross-sectional	50 Participants 18–35 years	Classified as obese, overweight, or normal based on BMI	What-where-when assessment (Treasure Hunter Task)	No	Higher BMI was associated with impaired performance on spatial, temporal, and item memory, as well as the ability to bind these elements together. Results were attenuated when considering demographic parameters
Cheke et al. (2017) [14]	Cross-sectional	34 Adults 18–36 years	Classified as obese or normal based on BMI	What-where-when assessment (Treasure Hunter Task), with brain activity assessed via fMRI	No	Compared to lean participants, obese participants had reduced functional neural activity in the angular gyrus, anterior prefrontal cortex, pre-cuneus, hippocampus, parahippocampal gyrus

Table 2 Quality rating of studies evaluating the association between obesity and memory function

Study	1	2	3	4	Total
Conforto and Gershman (1985)				×	1
Cournot et al. (2006)			×	×	2
Gunstad et al. (2006)				×	1
Dore et al. (2008)	×			×	2
Nilsson and Nilsson (2009)				×	1
Smith et al. (2010)	×	×	×	×	4
Gunstad et al. (2011)			×	×	2
Gonzales et al. (2012)				×	1
Katz et al. (2012)	×			×	2
Miller et al. (2013)			×	×	2
Alosco et al. (2014)			×	×	2
Boraxbekk et al. (2015)		×	×	×	3
Cheke et al. (2016)				×	1
Cheke et al. (2017)				×	1

Item 1: Was a criterion measure of obesity (i.e., not BMI) used?

Item 2: Were relevant covariates (i.e., both diet and exercise) included and evaluated in the analysis?

Item 3: Was a prospective or intervention design used?

Item 4: Were statistically appropriate/acceptable methods of data analysis used?

association between weight status and episodic memory function. One study demonstrated that the association between weight status and memory was attenuated after controlling for physical activity [85].

Some of the strongest evidence to support the obesity–memory relationship comes from the three prospective trials examining the effects of bariatric surgery on post-operative changes in memory function. All three trials [86–88] showed that when compared to obese controls, bariatric surgery among obese patients resulted in improved memory function, a finding that lasted up to 2 years post-surgery. Further, Smith et al. [89] demonstrated that those in the DASH Diet + WM (weight management) group had a reduction in weight and an improvement in memory after the 4-month intervention. This finding aligns with research in animal work showing that surgical lipectomy in mice completely normalizes hippocampus-dependent memory, long-term potentiation, and dendritic spine density [90]. Importantly, however, bariatric surgery may indirectly influence memory as surgery leads to a variety of cardiovascular and endocrine changes [91] that could influence memory function [34]. Thus, it is likely that obesity may influence episodic memory function, in part through pathways related to cardiovascular disease risk. For example, as noted in Fig. 1, some of the mechanisms (e.g., hypertriglyceridemia, insulin resistance, inflammation) linking obesity to memory function are cardiovascular disease risk factors.

At this point, it is uncertain as to whether the observed associations between weight status and episodic memory are adiposity driven, or moderated by physical activity behavior [92], dietary intake, or other lifestyle behaviors. There is, however, some evidence to suggest that both obesity and physical inactivity are independently associated with worse memory function [92]. This underscores the importance of future studies taking these lifestyle behaviors into account when examining the effects of weight status on memory function. In cross-sectional and prospective studies, this could be done via statistical adjustment and/or effect modification in the evaluated statistical models. For experimental studies, it would be worthwhile for future studies to experimentally manipulate changes in weight status via physical activity, diet, and surgery to determine what unique, if any, roles these manipulations have on changes in episodic memory. This will help provide more conclusive evidence as to whether adiposity itself is influencing memory changes, or rather, whether adiposity-related lifestyle behaviors are driving the obesity–memory relationship. Further, future work should aim to disentangle the interrelationships between obesity, cardiovascular disease risk factors, and episodic memory function. Such work should aim to overcome the methodological limitations of the majority of the studies on this topic. Given mixed findings [93, 94], additional work should extend this paradigm by also considering how these factors influence dementia risk from Alzheimer’s disease, as episodic memory decline is a hallmark characteristic of this disease [95, 96].

Compliance with ethical standards

Conflict of interest Author PL declares no conflicts of interest. Author EF declares no conflicts of interest.

Research involving human participants All procedures performed in studies 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.

Informed consent No consent was needed as this is a review paper.

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