

Genetically Predicted Body Mass Index and Alzheimer's Disease Related Phenotypes in Three Large Samples: Mendelian Randomization Analyses

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Abstract

Observational research shows that higher body mass index (BMI) increases Alzheimer's disease (AD) risk, but it is unclear whether this association is causal. We applied genetic variants that predict BMI in Mendelian Randomization analyses, an approach that is not biased by reverse causation or confounding, to evaluate whether higher BMI increases AD risk. We evaluated individual level data from the AD Genetics Consortium (ADGC: 10,079 AD cases and 9,613 controls), the Health and Retirement Study (HRS: 8,403 participants with algorithm-predicted dementia status) and published associations from the Genetic and Environmental Risk for AD consortium (GERAD1: 3,177 AD cases and 7,277 controls). No evidence from individual SNPs or polygenic scores indicated BMI increased AD risk. Mendelian Randomization effect estimates per BMI point (95% confidence intervals) were: ADGC OR=0.95 (0.90, 1.01); HRS OR=1.00 (0.75, 1.32); GERAD1 OR=0.96 (0.87, 1.07). One subscore (cellular processes not otherwise specified) unexpectedly predicted lower AD risk.

Keywords: obesity, dementia, Alzheimer's Disease, Mendelian randomization

INTRODUCTION

Observational studies indicate high midlife BMI predicts increased risk of Alzheimer's disease (AD), dementia, and memory impairment [1]. This association suggests weight management may reduce dementia risk, but the pattern may instead reflect confounding due to common causes of BMI and AD. Early life factors, such as cognitive characteristics,[2-3] socioeconomic status (SES),[4-5] and environmental toxins[6] potentially influence both BMI and AD risk. These factors are difficult to control in observational studies and may spuriously inflate associations between BMI and AD. Weight loss often occurs in prodromal stages of AD, leading to reverse causation, further obscuring causal effects.[7-8]

Causal effects of BMI on AD can be evaluated using "Mendelian Randomization" (MR) analyses, which are useful when reverse causation or confounding are likely.[9-11] In MR approaches, genetic variants that influence BMI are treated as a naturally occurring experiment in which some individuals, by virtue of their genetic inheritance, are "randomized" to higher BMI and others are randomized to lower BMI. As in randomized controlled trials, the overarching idea in MR is that randomization leads to differences in exposure (BMI) that are not related to confounding factors. MR takes advantage of accidents of meiosis – that is, each individual's inheritance of genes associated BMI is random. These genes are inherited independently of subsequent lifestyles or diseases unless the genes themselves influence such factors. The independence of these lifestyles and diseases from the genetic contribution to BMI enables unconfounded evaluations of associations between BMI and AD; these evaluations are thought to more closely approximate causal relationships because if the assumptions made by MR hold, the influence of confounding factors is substantially reduced or eliminated. MR analyses use genetic data to predict BMI, and assess associations between predicted BMI and AD. If BMI affects AD risk, then genetic factors that increase BMI should also increase AD risk (see further explanation of MR in [Supplemental Methods 1.1](#)). Because the effects of known alleles on BMI are relatively small, the magnitude of the association between BMI-related alleles and AD is also expected to be smaller than the association of BMI itself and AD. MR analyses account for this by using two stages of regression models to scale the association of BMI-related alleles and AD in proportion to the effect of these alleles on BMI.

In most MR studies, including analyses presented here, the genetic variants explain a small percentage of variance in measured phenotypes. The primary goal of MR is to avoid bias, even if there are unmeasured common causes of BMI and AD. The tradeoff for reducing bias is imprecise effect estimates. Combining information on multiple variants into polygenic scores improves precision, but null MR results are most convincing if they are from large samples.

We conducted MR analyses of associations between BMI and AD-related phenotypes using data from the AD Genetics Consortium (ADGC) and the Health and Retirement Study (HRS). We used published results from GERAD1 to provide a 3rd independent sample.[12] From the pool of BMI related variants, we defined 4 mechanism-specific genetic subscores and derived subscore-specific effect estimates.[13] We

hypothesized that BMI increases AD risk and that therefore the BMI polygenic scores and subscores would predict higher risk of AD-related outcomes.

METHODS

Sample 1: ADGC

The ADGC includes data from 19,692 individuals (10,079 AD cases and 9,613 cognitively normal elderly controls documented not to suffer from mild cognitive impairment) from 15 different studies, as previously published[14] and summarized in [Supplemental Methods 1.2](#). Websites for each study are detailed in [Supplementary eTable 1](#). Each study in the ADGC consortium genotyped using platforms from Illumina or Affymetrix and directly genotyped *APOE*. Each dataset was imputed to the HapMap build 132 reference panel.

Sample 2: HRS

The HRS is a nationally representative cohort with enrolments in 1992, 1993, and 1998. Biennial interviews (or proxy interviews for decedent or impaired participants) are available through 2010.[15-17] From 12,123 HRS participants with genetic data, we restricted analyses to 8,403 with self-reported European ancestry. Genotyping was completed on an Illumina platform and imputed to the 1000 Genomes reference panel (details in [Supplemental Methods 1.3](#)).

Sample 3: GERAD1

The GERAD Consortium included 3,177 AD cases and 7,277 controls confirmed to be free of dementia. Studies genotyped using various platforms and the dataset were imputed to the 1000 genome reference panel. We reanalyzed published data from GERAD1 [12] (see [Supplemental Methods 1.4](#)).

Outcome Measures

All ADGC cases met NINCDS-ADRDA criteria for definite, probable, or possible AD[18], and all controls were cognitively normal elders. In HRS, we considered two outcomes. We used a previously developed dementia probability score (probability individual meets DSM-IV criteria) that integrates proxy and direct cognitive assessments[19]. We also used memory outcomes comprising word list recall and proxy assessments averaged across up to 9 assessments.[17, 19] GERAD1 cases met criteria for probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD.[12]

BMI polygenic score generation

A previous meta-analysis of BMI genome wide association studies in 249,796 individuals identified 32 SNPs associated with BMI.[13] Following Richmond et al. [20], we used these genome-wide significant SNPs and the associated β weights from the published meta-analysis [13] to construct polygenic scores in ADGC (where 31 of the SNPs were available), and HRS (29 SNPs were available). For each individual i we calculated BMI polygenic scores, using an additive genetic model, as the sum across k SNPs of the product of the β weight for the effect of that SNP on BMI by the individual's allele count for that SNP:

(1)

In exploratory analyses, we assigned each gene to one of four functional categories to generate mechanism-specific subscores after a literature review in PubMed: adipogenesis (adipocyte differentiation and fat accumulation, e.g. rs3817334 (MTCH2) with HDL-cholesterol levels[21]), appetite (regulation of appetite and food intake, e.g. rs10767664 (BDNF) with total caloric intake[22]), cardiopulmonary factors (cardiomyogenesis, oxidative stress response and cardiac remodeling, e.g. rs1310732 (SLC39A8) with diastolic blood pressure[21]), and BMI-related processes not otherwise specified (groupings and supporting references are shown in [Supplemental eTable 2](#)).

Statistical analysis

As evidence for the validity of the MR analyses, we first used linear regression models to confirm that our polygenic scores predicted BMI in

two ADGC studies with available BMI data (Adult Changes in Thought [ACT] and Religious Orders Study/ Memory and Aging Project [ROS-MAP]), and in HRS. We confirmed that BMI polygenic scores are independent of age and sex.

In our primary MR analyses, we used each SNP and BMI polygenic scores to predict AD (ADGC) or dementia probability (HRS) in logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs). All models accounted for population stratification with 3 principal components for ADGC and 6 for HRS. ADGC models included terms for each of the 15 studies and HRS models included age and sex. In HRS, we used linear models for the memory outcome.

We performed over-identification tests, a standard approach to evaluating MR analyses,[23-25] by comparing effect estimates from the 4 mechanism-specific polygenic scores. If associations between mechanism-specific scores and AD risk are statistically different, this would imply either a direct pathway linking genetic variants to AD that is not mediated by BMI, or that the different genetic subscores influence distinct types of adiposity, which in turn have distinct consequences on AD.

We repeated overall and mechanism-specific analyses using results from a recently published study from the GERAD Consortium.[12] We estimate the MR based OR for the effect of BMI on AD using an inverse variance weighted approach[26] in GERAD and meta-analyzed ADGC and GERAD1 results, as both these consortia used AD as the outcome.

In addition we investigated non-linear effects of BMI on AD and dementia by backing out the genetically predicted BMI from the measured BMI in HRS and ROS-MAP.[27] We subsequently divided this new “environmental” BMI into three strata (Environmental BMI <20, 20 - <30, >30) and included this variable as an interaction term when predicting AD and dementia using the BMI polygenic score.

All participants in all studies signed consent forms, and review boards have approved the present analyses, as detailed in [Supplemental Methods 1.6](#).

All analyses were considered significant using a two-sided $\alpha = 0.05$ criterion, without correction for multiple testing.

RESULTS

Demographic characteristics of study participants are shown in [Table 1](#). In HRS, mean BMI was 27.4 Kg/m² (SD = 5.08); only 65 (0.7%) participants were underweight (BMI < 18.5), 2879 were (34.3%) normal weight (BMI: 18.5 – 25), 3327 (39.6%) were overweight (BMI: 25-30), and 2133 (25.4%) obese (BMI > 30). BMI polygenic scores predicted a range of 4.0 (mean=3.37, SD=0.55) BMI points in ADGC and a range of 3.7 (mean=3.87, SD=0.52) BMI points in HRS ([Table 2](#)). As expected under the analysis assumptions, BMI polygenic scores were independent of age (ADGC *p*-value = 0.48, HRS *p*-value 0.75) and sex (ADGC *p*-value = 0.87, HRS *p*-value 0.75). In 3,008 individuals with available BMI measures from ACT or ROS/MAP (of whom 615 eventually developed AD), BMI polygenic scores significantly predicted measured BMI at study entry ($\beta=0.86$; 95% confidence interval [CI] 0.53, 1.20; *p*-value < 0.001) and in HRS ($\beta=1.03$, 95% CI 0.83, 1.23, *p*-value <0.001)([Table 3](#)). As expected in these samples of older people, the gene score explained only a small proportion (~1%) of the variance in BMI. Each of the mechanism-specific polygenic scores also significantly predicted BMI ([Supplementary eTable 3](#)).

STUDY	Total	Cases	Controls	Sex (% male)	Age, mean (SD)
ADGC TOTAL	19,482	18,879	6,033	48.7	76.8 (5.96)
ACT	2,247	562	1,685	42.5	81.8 (5.95)
ADGC 1+2+3	4,325	3,122	1,203	44.8	74.4 (5.35)
ADGC	431	293	138	56.8	76.8 (6.75)
ROSMAP	1,208	689	519	39.8	74.5 (6.71)
MAYO	1,888	724	1,164	46.4	73.5 (4.40)
MEMPHIS	586	508	280	37.9	73.9 (6.49)
ROS-MAP	1,614	1,001	613	39.1	74.8 (7.50)
OHIO	279	128	151	42.9	85.9 (6.95)

Table 1
Demographic characteristics of participants in each ADGC contributing dataset and the HRS Study

Variable	Cases	Controls	Total
N, (%)	18,879 (95.2%)	6,033 (48.4%)	19,482 (98.4%)
BMI Polygenic Score, mean (SD)	3.37 (0.55)	3.30 (0.54)	3.37 (0.55)
Mechanism-Specific BMI Polygenic Score, mean (SD)			
Adipogenesis	0.63 (0.35)	0.67 (0.37)	0.65 (0.36)
Appetite	1.13 (0.42)	1.09 (0.40)	1.11 (0.41)
Carbohydrate	0.24 (0.30)	0.23 (0.30)	0.24 (0.30)
Unappetite/Calorie Intention	1.89 (0.25)	1.89 (0.25)	1.89 (0.25)

Table 2
Summary statistics for BMI polygenic scores (n=19,692)^a

Table 3
Linear regression coefficients for associations between BMI polygenic scores and measured BMI in ADGC (ACT, ROS-MAP)

Table 3
Linear regression coefficients for associations between BMI polygenic scores and ADGC (ACT, ROS-MAP) and HRS

ACT + ROS-MAP	n	β	95% Confidence Interval	P-value
All	1,008	0.00	(-0.10, 0.10)	<0.001
Controls	2,200	0.00	(-0.07, 0.07)	<0.001
AD Cases	615	0.00	(-0.10, 0.10)	0.10
HRS	1,008	0.00	(-0.10, 0.10)	0.00
Controls	1,047	0.04	(-0.10, 0.18)	0.01
AD Cases	344	-0.01	(-0.02, 0.02)	0.00

None of the genetic variants associated with BMI was associated with AD in ADGC or with probability of dementia or memory in HRS after Bonferroni correction (Table 4). Of particular note, neither of the BMI-related SNPs (rs4836133, rs713586) previously reported to have a nominal association with AD risk in GERAD [12] was associated with AD risk in ADGC; nor were they associated with probability of dementia or memory in HRS. Higher BMI polygenic scores were non-significantly associated with lower odds of AD (OR= 0.95, 95% CI: 0.90 - 1.01, p -value = 0.09) in ADGC as a whole (Table 5), and were not significantly associated with increased AD risk in any of the 15 studies within ADGC (Supplemental Results, eFigure 1). For ADGC, further adjustment for age, sex, and APOE ϵ 4 made little difference (Supplemental Results, eTable 4). In HRS, higher BMI polygenic scores were not associated with probability of dementia (OR: 1.00, 95%-CI: 0.75, 1.32, p -value = 0.98) or memory (beta = 0.002, 95%-CI: -0.01, 0.01, p -value = 0.57). In GERAD, the BMI polygenic score was not significantly associated with increased AD risk (Table 5, OR: 0.96, 95% CI: 0.87, 1.07). Fixed-effects meta-analysis of the ADGC and GERAD estimated ORs for the causal effect of BMI on AD was 0.95 (95%-CI: 0.91 - 1.00, p -value = 0.06) (Table 5).

Table 4
Association Analysis for validated BMI increasing SNPs and Alzheimer's Disease and Memory Function

Chr	SNP	Al	ADGC		HRS		GERAD	
			log(OR)	p	log(OR)	p	log(OR)	p
1	rs1050543	C	-0.01	0.432	0.014	0.320	-0.001	0.423
2	rs2090652	C	0.004	0.906	0.005	0.930	0.001	0.423
6	rs87227	G	0.01	0.542	-0.02	0.679	-0.001	0.308
10	rs4836133	C	0.02	0.483	0.003	0.565	0.00	0.784
11	rs713586	T	-0.01	0.406	-0.009	0.307	0.002	0.342
12	rs713586	A	0.00	0.999	-0.013	0.549	0.04	0.277

Table 4

Association Analysis for validated BMI increasing SNPs and Alzheimer's Disease, Dementia Probability, and Memory Function

Table 5
Genetic instrumental variable effect estimates: odds ratios for associations between BMI polygenic scores and AD (ADGC, GERAD) and Dementia Probability (HRS)^a

	ADGC			GERAD			ADGC + GERAD		
	OR	95% Confidence Interval	P	OR	95% Confidence Interval	P	OR	95% Confidence Interval	P
BMI Polygenic Score	0.95	(0.90, 1.01)	0.09	0.96	(0.87, 1.07)	0.48	0.95	(0.91, 1.00)	0.06
Mechanism Specific BMI Polygenic Scores									
Appetite	1.04	(0.87, 1.24)	0.61	1.00	(0.82, 1.20)	0.97	1.01	(0.80, 1.27)	0.93
Adiposity	0.82	(0.72, 0.92)	0.001	0.87	(0.46, 1.66)	0.68	0.82	(0.72, 0.92)	0.001
Cardio-Pulmonary Function	0.87	(0.87, 0.87)	0.11	0.81	(0.62, 1.06)	0.13	0.81	(0.74, 0.90)	<0.001

Table 5

Genetic instrumental variable effect estimates: odds ratios for associations between BMI polygenic scores and AD (ADGC, GERAD) and Dementia Probability (HRS)^a

The mechanism-specific polygenic scores for Appetite, Adiposity, and Cardio-Pulmonary Function were not significantly associated with AD in ADGC or GERAD, or with probability of dementia or memory in HRS (Table 5). The “Unspecified BMI-related Cellular Processes” polygenic score was associated with lower odds of AD in the ADGC (OR: 0.82, 95% CI: 0.72 – 0.92, p -value = 0.001), with lower probability of dementia (OR=0.87, 95% CI 0.46-1.66, p value = 0.68) and higher memory scores (β =0.02, 95% CI 0.00, 0.04, p value = 0.11) in HRS, and with lower AD risk in GERAD (OR: 0.81, 95%-CI: 0.62, 1.06, p value = 0.13). The forest plot for “Unspecified Cellular Processes” showed consistent effects across studies in ADGC and GERAD (Supplementary eFigure 2). The fixed-effects meta-analysis of ADGC and GERAD resulted in an OR of 0.81 (95%-CI: 0.74 - 0.90, p -value < 0.001). The over-identification test rejected the null hypothesis that the effect estimates for the 4 mechanism-specific subscores were identical in the ADGC (p -value = 0.01) but not for dementia probability (p = 0.30) or the memory outcome (p -value = 0.46) in HRS or for AD in GERAD (p -value=0.13).

In sensitivity analyses we tested whether the top 1000 BMI-increasing SNPs from Speliotes et al. were associated with higher dementia risk in our study cohorts. We found no evidence of association between this enlarged BMI polygenic score and AD (ROS-MAP, OR: 0.89, 95%-CI: 0.76 - 1.05), or dementia probability (HRS, OR: 1.03, 95%-CI: 0.94 - 1.12). Likewise, comparing the sign of the association with BMI (from GIANT) to the sign for the association with AD (from IGAP), we found no significant tendency for SNPs that predicted higher BMI also predicted higher AD risk (p =0.24). Results from the evaluation of a possible non-linear relationship between BMI and AD or dementia were inconclusive and are reported in the appendix (Supplementary eTable 5).

DISCUSSION

We find that a BMI polygenic score predicting a range of almost 4 points in BMI was not associated with increased risk of AD-related phenotypes in any of 3 large studies. Indeed, point estimates indicate lower dementia risk associated with higher BMI. In exploratory

analyses, polygenic scores relating to BMI differences induced by appetite, cardiopulmonary processes, and adipogenesis polygenic scores had null effects on risk of AD-related outcomes. In contrast, a polygenic score for genes influencing BMI via “unspecified cellular processes” significantly predicted lower risk of AD related phenotypes.

The link between obesity and dementia has long been controversial. A recent meta-analysis [1] concluded that midlife obesity (40-59 years) increases dementia risk. Reducing population obesity has therefore been proposed as a promising strategy to reduce the global burden of dementia[1, 28-29]. Obesity at older ages has been associated with lower risk of AD[30-31], however, an observation that is often attributed to reverse causation (early dementia reducing appetite, for example). Caution is warranted, however, because the inference that midlife BMI is harmful is based largely on observational studies, which face well-recognized methodological difficulties for establishing causality [11]. These limitations are especially salient when estimating effects of BMI on AD.

Because randomized trials of BMI are not feasible, however, until now there has been no practical approach to advance beyond conventional observational studies. This challenge therefore motivated the current analysis, which is not vulnerable to the same confounding or reverse causation bias. Using MR avoids bias even if there is reverse causation. MR also avoids bias from measured or unmeasured confounders that may influence both BMI and AD, such as childhood SES. Although all epidemiologic studies must rely on strong assumptions to support causal inferences, the MR approach we present here offers a powerful tool to evaluate causal hypotheses and is an important step forward with the goal of a triangulation of evidence. MR can uncover risk factors even if the critical etiologic period occurs prior to study enrollment. [32-34] The BMI estimate derived here probably best corresponds with a lifelong difference in BMI, incorporating early and midlife differences. Our results suggest the simplistic view -- that elevated BMI increases dementia risk -- may be misguided.

Our findings are consistent with two possible interpretations. One is that BMI does not affect AD risk, and previous findings are due to uncontrolled confounders. Another possibility is that BMI is a multi-faceted exposure capturing different dimensions of adiposity, and these different dimensions have distinct effects on dementia risk. This latter interpretation is consistent with evidence that BMI is influenced by heterogeneous physiologic characteristics, for example including both lean and fat body mass and peripheral and central adiposity.[35-36]

MR analyses rely on three assumptions: the genes must predict the phenotype of interest (e.g., BMI); there must be no *direct* pathway from the genes to the outcome not mediated by the phenotype (i.e., no pleiotropic effects of the BMI related genes on AD); and there must be no common causes of the genes and the outcome (e.g., genes in linkage disequilibrium with the BMI alleles that themselves influence AD). Although assumptions of MR analyses merit careful scrutiny[23], the most plausible violations of these assumptions seem unlikely to account for our findings. Extensive prior evidence supports the first assumption, that the BMI polygenic score predicts life course BMI of participants. We used only SNPs previously shown to predict BMI at genome-wide significance thresholds and confirmed that our polygenic score predicted BMI in HRS, ACT, and ROS/MAP. The second assumption, that the variants used in the polygenic score have no direct pathways via which they influence AD *except through* BMI, cannot be proven. Nevertheless, there is strong supporting evidence. For example, recent findings of Hinney et al, showed only two BMI-related SNPs had a suggestion of a direct effect on AD (neither survived Bonferroni correction) [12]. These SNPs were not associated with AD in ADGC or dementia in HRS. This does not conclusively prove the validity of our approach, but we note that even if there is modest pleiotropy, it is unlikely to explain our unexpected null associations. To explain the discrepancy between our results and observational findings, there must be variants that *increase* BMI but *decrease* AD risk. Nonetheless the assumption that there is no direct relationship between our BMI variants and AD requires scrutiny and replication of our findings is needed. The third MR assumption (no unmeasured common causes of the genetic variants and AD) is generally least controversial because conceptually most AD risk factors are temporally subsequent to genetic background and therefore few risk factors are plausible causes of the genetic variants. However, this assumption could be violated, for example, if parental genotype on the loci in our BMI polygenic scores influenced participants’ SES, which influenced AD risk. Given associations between SES and BMI, this seems possible, but unlikely to explain our results because any effects would bias towards associations between higher BMI and increased AD risk (whereas we found non-significantly reduced risk).

One caveat to our analyses is that BMI may be relevant for AD only above a certain threshold. The BMI polygenic score shifts the entire distribution of BMI, so it is associated with increased risk of being above any particular threshold (e.g., BMI>30 or BMI>35). For example, each unit on the polygenic score was associated with an OR of 1.50 (95% CI: 1.36, 1.65) for obesity among HRS participants. Even if the effect of adiposity only occurs above a threshold, we would expect the polygenic score to predict higher AD risk. Nonetheless, our point estimates should be interpreted cautiously for several reasons [37-39], including the lifelong effects of the genetic factors on BMI and the use

of a case-control design. These factors could not, however, account for the null or protective association between the polygenic score and AD if BMI were in fact harmful. Another concern is related to survivor bias. Both ADGC and the GERAD1 sample are AD case control studies among older individuals. BMI has strong and age-dependent links to mortality[40], thus our samples may have included a highly selected subgroup of “survivors” immune to the effects of obesity. A very similar bias should apply to conventional observational studies, however, so it is unlikely that this bias could explain differences between our results and previous work.

MR can identify potentially heterogeneous effects of different dimensions of adiposity influenced by variants in different genes, even if these differences in adiposity were not directly measured. This is extremely appealing because the limitations of BMI are widely acknowledged. [35-36, 41]. MR estimates are specific to the phenotype influenced by the variants used in the analysis. We found evidence that a set of genetic variants associated with higher BMI may slightly reduce AD risk. This result was surprising, but if confirmed elsewhere, it could provide powerful insights into the origins of dementia and the link with adiposity. We consider the finding with respect to subscore effects to be exploratory, particularly because of the uncertainty in the causal genes associated with each SNP[42]. For example, recent findings from Smemo et al. suggest that the effects of the SNPs identified in intronic regions of the FTO locus in fact regulate expression of the IRX3 locus, rather than FTO. Our allocation of these SNPs to the “appetite” subscore was due to evidence that FTO expression regulates appetite and that the SNPs correlated with dietary intake, including selection of energy dense foods.[43-45] IRX3, however, is hypothesized to influence obesity via energy homeostasis, calling into question whether these SNPs should be classified as operating via an “appetite” mechanism. [46]

An important strength of this paper is that we derived the BMI polygenic score from SNPs identified in an external dataset. The proportion of variance in observed BMI explained by the BMI polygenic score was small. Nevertheless, since SNPs and their weights were derived externally, concerns of “weak instruments bias” are eliminated.[38, 47] Consistency of findings across 3 samples is another notable strength. Statistical power is a common limitation in MR analyses, but the CIs in our analyses are informative and exclude any but very tiny harmful effects of BMI.

In summary, our finding that polygenic scores strongly related to higher BMI are unrelated to dementia risk and may even predict lower dementia risk is surprising, given prior observational evidence linking BMI and AD. Replication of this result in independent samples, and analyses to evaluate the assumptions of the MR approach for this research question are needed. These MR results, if confirmed, would suggest greater complexity in the link between adiposity and AD than previously understood.

Systematic Review

Previous research links elevated Body Mass Index (BMI) and other measures of obesity to increased risk of Alzheimer’s disease (AD) and dementia, but all prior studies are based on similar, observational, study designs. Observational study designs may be biased because unmeasured confounders influence both obesity and dementia risk.

Interpretation

We used a new study design, “Mendelian Randomization”, to test whether obesity affects dementia or AD. We combined information on multiple genetic differences that predict higher BMI into a score for genetically induced BMI. The genetic score for higher BMI did not predict risk of AD or dementia in any of three samples, and one subscore unexpectedly appeared protective. Results suggest BMI may not substantially increase dementia risk. Some aspects of adiposity may even protect against dementia.

Future Directions

Future studies should focus on alternative study designs to evaluate the causal links between adiposity and dementia.

Supplementary Material

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Alzheimer's Disease Genetics Consortium

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Footnotes

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