Body Mass Index and Risk of Alzheimer's Disease: A Mendelian Randomization Study of 399,536 Individuals

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Context: Recently, data on 2,000,000 people established that low body mass index (BMI) is associated with increased risk of dementia. Whether this observational association reflects a causal effect remains to be clarified.

Objective: We tested the hypothesis that there is a causal association between low BMI and high risk of Alzheimer's disease.

Design, Setting, and Participants: Using a Mendelian randomization approach, we studied 95,578 individuals from the Copenhagen General Population Study (CGPS) with up to 36 years of follow-up and consortia data on 303,958 individuals from the Genetic Investigation of Anthropometric Traits (GIANT) and the International Genomics of Alzheimer's Project (IGAP).

Main Outcome Measure: Risk of Alzheimer's disease.

Results: The causal odds ratio for a 1-kg/m^2 genetically determined lower BMI was 0.98 [95% confidence interval (CI), 0.77 to 1.23] for a weighted allele score in the CGPS. Using 32 BMI-decreasing variants from GIANT and IGAP the causal odds ratio for Alzheimer's disease for a 1-standard deviation (SD) lower genetically determined BMI was 1.02 (95% CI, 0.86 to 1.22). Corresponding observational hazard ratios from the CGPS were 1.07 (95% CI, 1.05 to 1.09) and 1.32 (95% CI, 1.20 to 1.46) for a 1-kg/m^2 and a 1-SD lower BMI, respectively.

Conclusions: Genetic and hence lifelong low BMI is not associated with increased risk of Alzheimer's disease in the general population. These data suggest that low BMI is not a causal risk factor for Alzheimer's disease and that the corresponding observational association likely is explained by reverse causation or confounding. (***J Clin Endocrinol Metab*** **102: 2310–2320, 2017)**

Understanding the association between body mass index (BMI) and dementia is becoming a public health priority due to increasing prevalence of dementia and obesity worldwide (1–3). Both obesity and underweight have been associated with increased risk of dementia, and these discordant findings appear to be dependent on the age at which obesity was recorded (4–8). Recently, data on 2,000,000 people from the UK Clinical Practice Research Datalink (CPRD) established that low BMI is associated with increased risk of dementia throughout the age range (9). Whether this observational association reflects a causal effect remains to be clarified.

Despite the recent strong observational evidence between low BMI and increased risk of dementia (9), such

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Abbreviations: BMI, body mass index; CGPS, Copenhagen General Population Study; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GIANT, Genetic Investigation of Anthropometric Traits; ICD, International Classification of Diseases; IGAP, International Genomics of Alzheimer's Project; SD, standard deviation.

data cannot overcome the problems of reverse causation and confounding, and therefore do not have the ability to establish causality (10). Dementia, or cognitive impairment prior to establishment of the dementia diagnosis, may lead to low BMI—so-called reverse causation. Alternatively, the observational association may be due to confounding, for instance if another factor simultaneously decreases BMI and causes dementia, leaving BMI as a marker of this other causal factor.

Mendelian randomization is an epidemiological approach that aims to avoid reverse causation and confounding by using genetic variants in human populations. Because genetic variants are determined at conception and remain constant throughout life, Mendelian randomization is not influenced by reverse causation; for instance, dementia cannot change the genotype of an individual (10). Furthermore, because random assortment of alleles occurs during conception, genetic variants with effect on a modifiable exposure, for example BMI, are randomly distributed in relation to potential confounders. In other words, genetic variants that are associated with low BMI can be used as unconfounded proxies to study the effect of lifelong low BMI on outcomes. Thus, if low BMI truly is a causal factor in the development of dementia, genetic variants that cause low BMI would be expected to also cause high risk of dementia.

Using a Mendelian randomization design, we tested the hypothesis that there is a causal association between low BMI and high risk of Alzheimer's disease, the most common form of dementia. First, we tested whether low BMI at baseline was associated prospectively with high risk of Alzheimer's disease. Second, we tested whether BMI-decreasing alleles of *FTO* rs9939609, *MC4R* rs17782313, *TMEM18* rs6548238, *BDNF* rs10767664, and *GNPDA2* rs10938397 were associated with low BMI, as expected (11). Third, we tested whether BMI-decreasing alleles were associated directly with high risk of Alzheimer's disease, and fourth, whether the effect of BMI-decreasing alleles on risk of Alzheimer's disease, using instrumental variable analysis, was consistent with the observational association between BMI and risk of Alzheimer's disease. Finally, we tested these associations in the BMI and Alzheimer disease consortia, the Genetic Investigation of Anthropometric Traits (GIANT) and the International Genomics of Alzheimer's Project (IGAP), including a total of 399,536 individuals.

Materials and Methods

The study was approved by institutional review boards and Danish ethical committees (H-KF-01-144/01) and was conducted according to the Declaration of Helsinki with written informed consent from participants. All participants were white and of Danish descent.

Participants

The Copenhagen General Population Study (CGPS) is a study of the general population initiated in 2003 with ongoing enrollment (12–15). Participants were randomly selected from the national Danish Civil Registration System to reflect the adult general population aged 20 to 100+ years. Data collection included a questionnaire, a physical examination, and blood sampling for biochemical analyses and DNA extraction. We included 95,578 participants in the present analyses, of whom 645 developed Alzheimer's disease and 3,281 developed type 2 diabetes, the latter used as a positive control.

Disease endpoints

Information on diagnoses of Alzheimer's disease was collected from the national Danish Patient Registry with data on all patient contacts from all clinical hospital departments in Denmark since 1977, including emergency wards and outpatient clinics from 1995, and from the national Danish Causes of Death Registry with data on causes of all deaths in Denmark, as reported by hospitals and general practitioners since 1977. Alzheimer's disease was World Health Organization International Classification of Diseases (ICD) ICD8 290 and ICD10 F00 and G30. The validity of Alzheimer's disease ICD codes from the Danish registries is high (16), and was further ensured by the presence of the well-known association with the apolipoprotein E $\varepsilon 4$ allele in the present cohort (14). The prevalence of Alzheimer's disease in the CGPS is in accordance with the estimated prevalence from the National Dementia Research Centre (17). Information on diagnoses of type 2 diabetes (World Health Organization; ICD-8 250; and ICD-10, E11 E13 and E14) was collected similarly, and was used as a positive control. Follow up began at the time of blood sampling (observational analyses) or at the establishment of the national Danish Patient Registry (January 1st, 1977) or on the birthday of the participant, whichever came later (genetic analyses). Follow up ended at occurrence of event, death, emigration, or on November 10th 2014 (last update of registries), whichever came first. Median follow-up was 7 years (range: 0 to 10 years) and 36 years (range: 0 to 37 years) in observational and genetic analyses, respectively, and was 100% complete, that is, no individual was lost to follow-up. Individuals with events before study entry were excluded from the observational analyses.

Biochemical and genetic analyses

Standard hospital assays measured total cholesterol, high-density lipoprotein cholesterol and triglycerides (Boehringer Mannheim, Mannheim, Germany). Low-density lipoprotein cholesterol was calculated using the Friedewald equation (18) when plasma triglycerides were $\leq$ 4 mmol/L ($\leq$ 352 mg/dL), and otherwise measured directly (Konelab). An ABI prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) and Taqman-based assays were used to genotype for *FTO* rs9939609, *MC4R* rs17782313, *TMEM18* rs6548238, *BDNF* rs10767664, and *GNPDA2* rs10938397 (11). We chose these five genetic variants because they have the strongest association with BMI in the general population out of a total of 32 variants (11). Combining all genotypes, we generated two different genetic instruments for BMI. The first genetic instrument was calculated for each participant using a weighted sum of BMI-decreasing alleles (19, 20), subsequently

categorized into four groups of approximately equal size, named weighted allele score group. The weights correspond to the sum of the individual β-coefficients for the BMI-decreasing alleles in each individual adjusted for age and sex (Supplemental Table 1). The second genetic instrument was a simple counting of the number of BMI-decreasing alleles in each individual, subsequently categorized into four groups of approximately equal size, named simple allele score group.

BMI and covariates

All covariates are from the day of enrollment in 2003 and onwards. BMI was measured weight (kg) divided by measured height squared (m^2). Hypertension was use of antihypertensive medication and/or a systolic blood pressure of 140 mm Hg or greater, and/or a diastolic blood pressure of 90 mm Hg or greater. Diabetes mellitus was self-reported disease, use of insulin or oral hypoglycemic agents, and/or nonfasting plasma glucose levels of $>$ 11 mmol/L. Smoking was current smoking. Alcohol consumption was $>$14/21 units per week for women/men [1 unit = 12 g alcohol, equivalent to one glass of wine or one beer (33 cL)]. Physical inactivity was $\leq$4 hours per week of light physical activity in leisure time. Women reported menopausal status and use of hormonal replacement therapy. Lipid-lowering therapy was primarily statins (yes/no), and education was $<$ 8 years of education.

Consortia data

We downloaded summary estimates of genetic variants with effect on BMI in up to 249,796 individuals (11) from the GIANT consortium and obtained summary estimates on risk of Alzheimer's disease for the same BMI-decreasing variants in up to 54,162 individuals from the IGAP consortium. The GIANT consortium is an international collaboration that seeks to identify genetic loci that modulate human body size and shape, including height and measures of obesity. IGAP is a large two-stage study based upon genome-wide association studies on individuals of European ancestry. We used data from stage 1, where IGAP has genotyped and imputed data on 7,055,881 single nucleotide polymorphisms to meta-analyze four previously published genome-wide association study datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (the European Alzheimer's Disease Initiative, the Alzheimer Disease Genetics Consortium, the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium, and the Genetic and Environmental Risk in Alzheimer Disease Consortium).

Statistical analysis

Data were analyzed using Stata/SE version 13.0 and 14.0 (Stata Corp., College Station, TX). P values $<$0.001 are given as powers of 10. Chi-square test evaluated Hardy–Weinberg equilibrium. For trend tests, subjects were coded by BMI in quartiles or by weighted/simple allele score group as 1, 2, 3, and 4 with first quartile, group 1, or 0 to 3 as reference groups.

First, in observational analyses to examine the association between BMI levels and risk of Alzheimer's disease, we used Cox proportional hazards regression models with age as time-scale and delayed entry (left truncation) to estimate hazard ratios with 95% confidence intervals (CIs). On a continuous scale, the relationship between BMI and Alzheimer's disease was evaluated with the use of restricted cubic splines. The number of five knots was chosen to balance best fit and overfitting (21). Models were multifactorially adjusted for age (as time scale), sex, hypertension, diabetes, smoking, alcohol intake, physical inactivity, postmenopausal status and hormonal replacement therapy in women, lipid-lowering therapy and educational level. Trend tests were according to Cox regression trend test. Second, to assess whether weighted/simple allele score group was associated with BMI levels, we used linear regression. We used the hazard ratio for a 1-kg/m^2 decrease in BMI in the observational analysis to calculate theoretically predicted risks of Alzheimer's disease corresponding to the changes in BMI caused by weighted/simple allele score group. Third, in genetic analyses, we examined the association between weighted/simple allele score group and risk of Alzheimer's disease using Cox proportional hazards regression models with multifactorial adjustment. In sensitivity analyses, we determined hazard ratios for Alzheimer's disease for the individual genetic variants. In further sensitivity analyses, we tested for interaction between weighted/simple allele score group and covariates (as described previously) on Alzheimer's disease. Interaction between these covariates and weighted/simple allele score group on risk of Alzheimer's disease was evaluated by the inclusion of two-factor interaction terms in the Cox regression model, using a likelihood ratio test between models excluding and including the interaction term.

A potential causal relationship between genetically low BMI and risk of Alzheimer's disease was assessed by instrumental variable analysis (22) using "ivreg2" and "ivpois" in Stata. Finally to improve statistical power, we examined the association between genetically low BMI and risk of Alzheimer's disease in independent cohorts by including data from the GIANT and IGAP consortia. We used the inverse-variance weighted method (23) to calculate a causal odds ratio for Alzheimer's disease for a 1–standard deviation (SD) decrease in BMI.

Results

Baseline characteristics of the 95,578 study participants by Alzheimer's disease status are shown in Table 1. During up to 36 years of follow-up, we observed 645 Alzheimer's disease events and 3956 deaths; 159 individuals died with Alzheimer's disease. Median age was 76 (interquartile range = 70 to 80) and 58 (interquartile range = 48 to 67) years for those with and without Alzheimer's disease, respectively, reflecting that Alzheimer's disease is a disease of the elderly.

BMI and risk of Alzheimer's disease: observational estimate

Risk of Alzheimer's disease increased stepwise as a function of decreasing BMI in quartiles (P for trend = 5×10^{-7}; Fig. 1). For individuals in the fourth (lowest BMI) vs the first quartile (highest BMI), the hazard ratio was 1.89 (95% CI, 1.46 to 2.43) for Alzheimer's disease. For World Health Organization–defined categories,

Table 1. Characteristics of Study Participants in the CGPS

	Without Alzheimer's Disease	Alzheimer's Disease
Number of individuals, %	94,933 (99.3)	645 (0.7)
Age, y	58 (48 to 67)	76 (70 to 80)[i]
Female, %	55	58
Total cholesterol, mmol/L	5.6 (4.9 to 6.3)	5.7 (5.0 to 6.5)[j]
LDL cholesterol, mmol/L	3.2 (2.6 to 3.9)	3.2 (2.6 to 3.9)
HDL cholesterol, mmol/L	1.6 (1.3 to 1.9)	1.7 (1.4 to 2.1)[i]
Triglycerides, mmol/L	1.4 (1.0 to 2.1)	1.4 (1.0 to 2.0)
BMI, kg/m^2	26 (23 to 28)	25 (23 to 28)[j]
Hypertension,[a] %	60	83[i]
Diabetes mellitus,[b] %	4	8[i]
Smoking,[c] %	18	18
Alcohol consumption,[d] %	18	19
Physical inactivity,[e] %	49	60[i]
Postmenopausal,[f] %	67	99[i]
Hormonal replacement therapy,[f] %	16	18
Lipid-lowering therapy,[g] %	12	20[i]
Education <8 y,[h] %	10	32[i]

Values are median (interquartile range) or percent, and are from the day of enrollment in 2003 and onwards for CGPS. Missing values (0.6%) were imputed.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]Hypertension was use of antihypertensive medication and/or a systolic blood pressure of 140 mm Hg or greater, and/or a diastolic blood pressure of 90 mm Hg or greater.

[b]Diabetes mellitus was self-reported disease, use of insulin or oral hypoglycemic agents, and/or nonfasting plasma glucose levels of >11 mmol/L.

[c]Smoking was current smoking.

[d]Alcohol consumption was >14 units per week for women and 21 units per week for men [1 unit = 12 g alcohol, equivalent to one glass of wine or one beer (33 cL)].

[e]Physical inactivity was ≤4 hours per week of light physical activity in leisure time.

[f]Women reported menopausal status and use of hormonal replacement therapy.

[g]Lipid-lowering therapy was primarily statins (yes/no).

[h]Education was <8 years of education.

[i]$P < 0.001$ and [j]$P < 0.05$ by Mann-Whitney U test or Pearson's χ^2 test for Alzheimer's disease vs no Alzheimer's disease.

the results were similar (Supplemental Fig. 1). Using cubic restricted splines, we observed similar associations on a linear scale (Supplemental Fig. 2).

Genotype and BMI

BMI levels decreased stepwise with increasing weighted/simple allele score group of up to 2.8% (P for trend = 10^{-4})

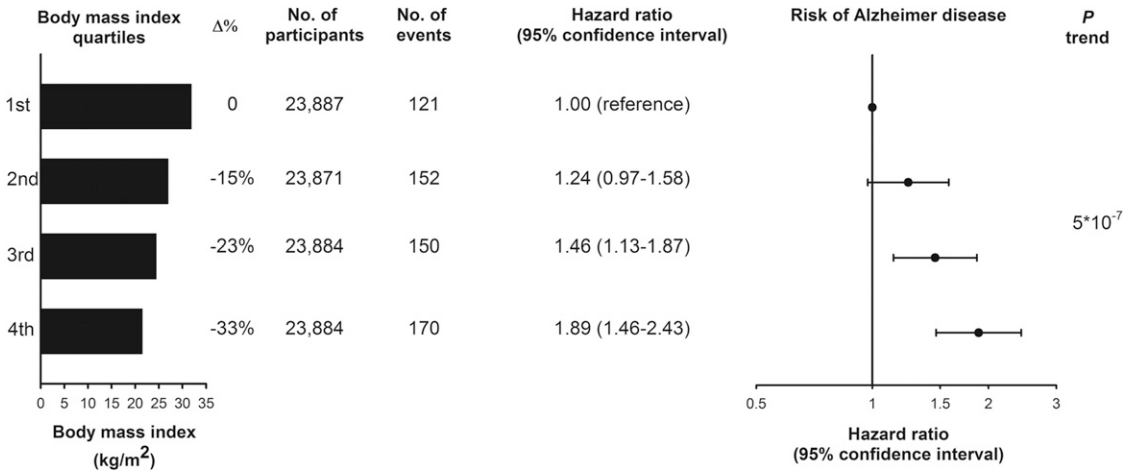

Figure 1. Risk of Alzheimer's disease as a function of BMI in quartiles in the CGPS. Individuals with Alzheimer's disease before blood sampling were excluded, leaving 95,526 individuals for this analysis. Multifactorial adjustment was for age (as time scale), sex, hypertension, diabetes, smoking, alcohol intake, physical inactivity, postmenopausal status and hormonal replacement therapy in women, lipid-lowering therapy and educational level. P for trend from Cox regression trend test.

for individuals in group 4 vs 1 or group 6 to 10 vs 0 to 3 (Fig. 2, left panel).

Genotype and risk of Alzheimer's disease

The 2.8% decreases in BMI in weighted allele score group 4 vs 1 and in individuals with simple allele score group 6 to 10 vs 0 to 3 theoretically predicted increased hazard ratios of 1.05 for Alzheimer's disease (Fig. 2, upper middle panel). However, neither the weighted allele score nor the simple allele score group was associated with risk of Alzheimer's disease (*P* for trend = 0.37 and 0.52; Fig. 2, upper right panel). In sensitivity analyses, the lack of association with Alzheimer's disease remained across individual genetic variants and strata of Alzheimer's disease risk factors (Supplemental Figs. 3–5).

BMI is causally associated with risk of type 2 diabetes. Therefore, to test our method using a positive control, we examined the association between weighted/simple allele score group and risk of type 2 diabetes. The 2.8% lower BMI in weighted allele score group 4 vs 1 and in simple allele score group 6 to 10 vs 0 to 3, theoretically predicted hazard ratios of 0.91 (95% CI, 0.90 to 0.92) for type 2 diabetes (Fig. 2, lower panel). The corresponding observed hazard ratios for type 2 diabetes were 0.84 (95% CI, 0.76 to 0.92) for both weighted and simple allele score group, indicating a causal relationship (*P* for trend = 6×10^{-5} and 3×10^{-4}).

Genotype and potential confounding factors

We tested whether potential confounding factors were associated with observational BMI, Alzheimer's disease, and weighted/simple allele score group. Age, sex, hypertension, physical activity, education, and menopause were all strongly associated with BMI and risk of Alzheimer's disease and thus constitute potential confounders for the observational BMI–Alzheimer's

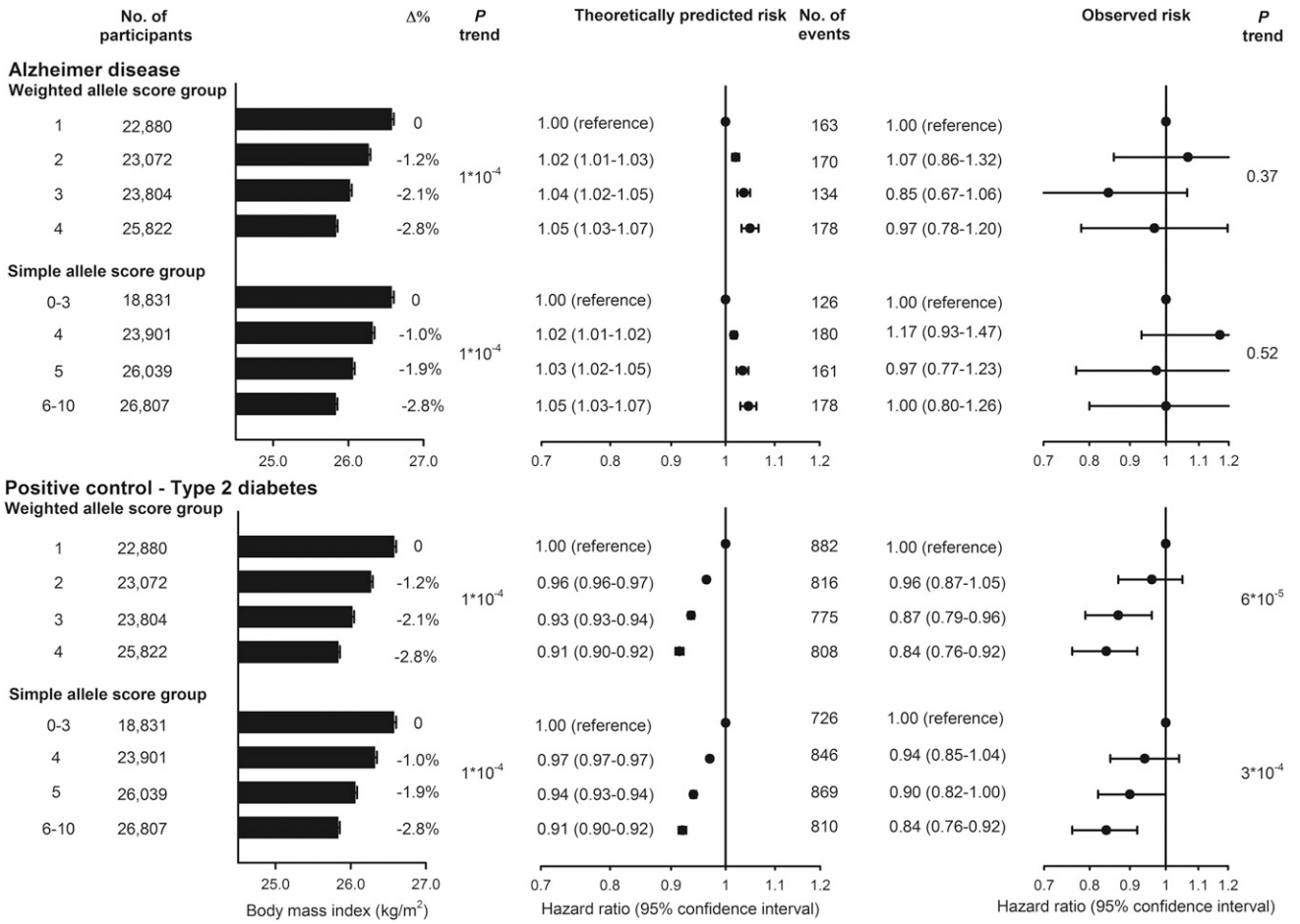

Figure 2. BMI (left) and corresponding theoretically predicted (middle) and observed (right) hazard ratios for Alzheimer's disease as a function of BMI weighted allele score/simple allele score group. Theoretically predicted hazard ratios were calculated from delta BMI and the known association of BMI with risk of Alzheimer's disease in the observational study (see Fig. 1). Observed hazard ratios were multifactorially adjusted for age (as time scale), sex, hypertension, diabetes, smoking, alcohol intake, physical inactivity, postmenopausal status and hormonal replacement therapy in women, lipid-lowering therapy, and educational level. As a positive control, estimates were also presented for type 2 diabetes (lower part of Fig. 2; multifactorial adjustment omitted diabetes as a covariate). BMI values are mean (±standard error of the mean). *P* values are test for trend.

disease association. In contrast, weighted/simple allele score group was not associated with any of these potential confounders, except for hypertension (Fig. 3, two right panels).

BMI and Alzheimer's disease: causal estimates

We examined the potential causal effect of low BMI on risk of Alzheimer's disease in instrumental variable analyses (Fig. 4). Causal odds ratios for a 1-kg/m^2 genetically determined lower BMI were 0.98 (95% CI, 0.77 to 1.23) for weighted allele score group and 1.01 (95% CI, 0.83 to 1.22) for simple allele score group (Fig. 4). The corresponding observational multifactorially adjusted hazard ratio for Alzheimer's disease for a 1-kg/m^2 lower BMI was 1.07 (95% CI, 1.05 to 1.09). The statistical strength of the weighted allele score was an *F* value of 140. To test our method using a positive control, we also examined the causal effect of low BMI on risk of type 2 diabetes in instrumental variable analyses. Causal odds ratios for a 1-kg/m^2 genetically determined lower BMI were 0.77 (95% CI, 0.61 to 0.98) for weighted allele score group and 0.85 (95% CI, 0.73 to 0.99) for simple allele score group (Fig. 4, lower panel). The corresponding observational multifactorially adjusted hazard ratio for type 2 diabetes for a 1-kg/m^2 lower BMI was 0.88 (95% CI, 0.87 to 0.89), indicating a causal relationship as expected.

Finally, when using data from 32 BMI-decreasing genetic variants from the GIANT and IGAP consortia (Supplemental Table 2), the estimated causal odds ratio for Alzheimer's disease for a 1-SD lower genetically determined BMI was 1.02 (95% CI, 0.86 to 1.22). The corresponding observational multifactorially adjusted hazard ratio for Alzheimer's disease for a 1-SD lower BMI was 1.32 (95% CI, 1.20 to 1.46; Fig. 5, upper panel). Further, we plotted the change in Alzheimer's disease risk as a function of change in BMI per allele for each of the 32 genetic variants and graphically illustrated the overall causal estimate (Fig. 5, lower panel).

Discussion

The principal finding of this study is that lifelong low BMI due to genetic variation in BMI-related genes is not associated with increased risk of Alzheimer's disease, in contrast to the observational association. We generated these results by combining large scale prospective data from a homogenous general population study with the current most powerful genetic data on BMI and Alzheimer's disease obtained from international consortia. The discordance between the observational and genetic estimates suggests that low BMI *per se* is not a causal risk factor for Alzheimer's disease, and that the observational association may be due to reverse causation or confounding.

The existing literature concerning BMI and Alzheimer's disease is conflicting. Previous studies and a recent meta-analysis concluded that midlife obesity increases dementia risk (4–6, 24), whereas obesity at older ages is associated with lower risk of Alzheimer's disease (4, 25). Recently, large-scale population evidence from

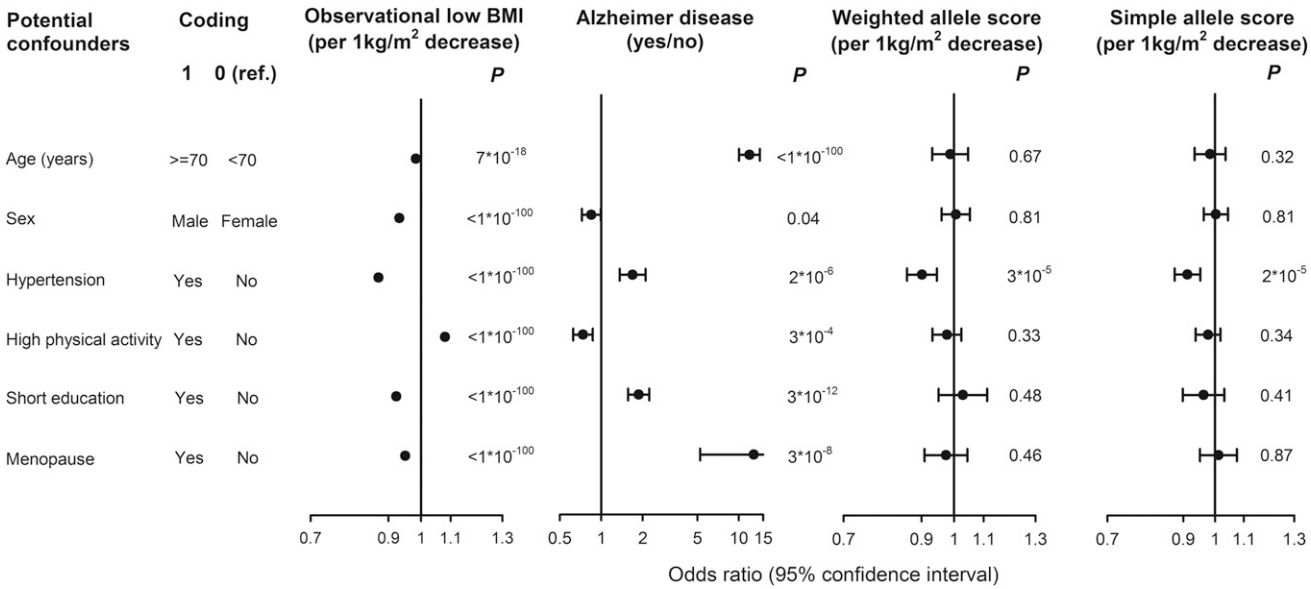

Figure 3. Association of potential confounders with BMI, Alzheimer's disease, and BMI weighted allele score/simple allele score group. Potential confounders were dichotomized: age (≥70 vs <70); sex (male vs female), hypertension (hypertension vs no hypertension), physical activity (high vs low physical activity), education (short, <8 years, vs long education), and menopausal status (postmenopausal vs premenopausal). Potential confounders were defined as described in the Table 1 footnote. For each potential confounder, logistic regression analysis was used to calculate sex- and age-adjusted odds ratios and *P* values for, respectively, a 1-kg/m^2 lower observational BMI, Alzheimer's disease vs no event, and a 1-kg/m^2 genetically lower BMI for weighted/simple allele score group.

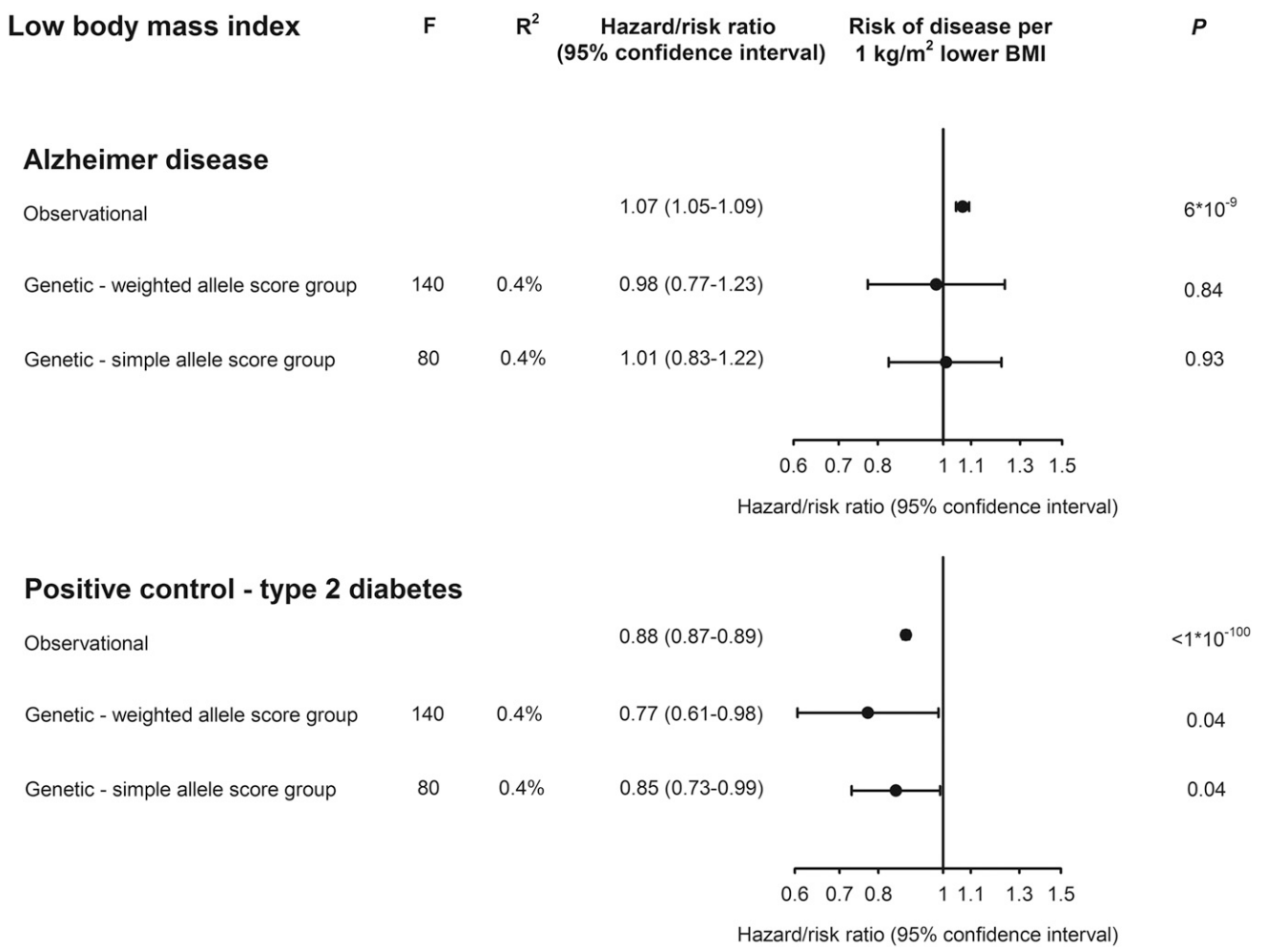

Figure 4. Risk of Alzheimer's disease for a 1-kg/m^2 lower observational and causal genetically determined BMI. The hazard ratio for a 1-kg/m^2 lower observational BMI was calculated using Cox regression, whereas the odds ratio for genetically low BMI was derived from an instrumental variable analysis. *P* value: significance of hazard ratio or odds ratio. F, strength of the genetic instrument (>10 indicates sufficient strength); R^2, percent contribution of genetic instrument to the variation in BMI.

the UK CPRD study reported that low BMI in all age groups was associated with high risk of Alzheimer's disease (9). These conflicting results reflect well-known problems in observational epidemiology, where associations are prone to confounding and reverse causation—the latter of special concern when estimating effects of BMI and Alzheimer's disease. It is well-known that early prodromal phases of dementia cause loss of initiative and apathy and changes in eating behavior, appetite, olfactory function, and food choice, all leading to a reduced caloric intake and thereby weight loss (8, 26). Therefore, reverse causation may be a likely explanation for the observed association between low BMI and high risk of dementia in the current study as well as in the UK CPRD study (9). To overcome the inherent limitations of observational epidemiology, we used the Mendelian randomization approach, a design that uses genetic variants that are associated with low BMI as instruments to examine the effect of lifelong low BMI on risk of Alzheimer's disease. We found that observational low BMI was associated with high risk of Alzheimer's disease, but with no genetic evidence to support corresponding causal relationships. The present negative findings are in line with genome-wide association studies and meta-analyses, which did not detect any associations between BMI related genes and Alzheimer's disease (27–29) and in line with two recent case-control studies also using consortia data that found no causal association between BMI and risk of Alzheimer's disease (30, 31).

Several biological explanations for the observational association between BMI and Alzheimer's disease have been suggested. Concerning midlife obesity and Alzheimer's disease, a plausible link could be obesity-related vascular disease such as hypertension and stroke, as well as alterations in brain structure, white matter changes, and blood–brain barrier disturbances (32–34). Furthermore, adipokines—defined as hormones, cytokines, and peptides secreted by adipose tissue—have been suggested to have widespread influence and functionality in the brain (35). Especially, leptin, adiponectin, and interleukin-6 are

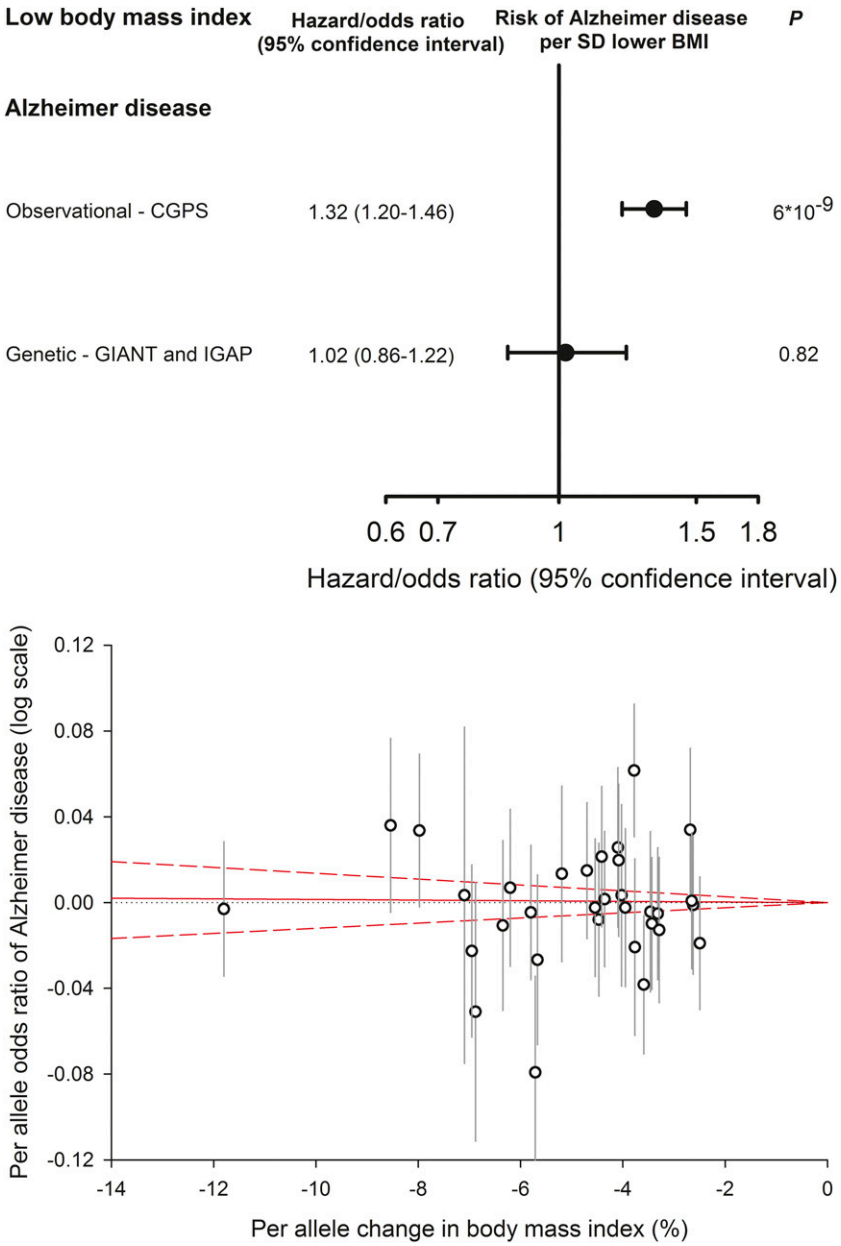

Figure 5. Risk of Alzheimer's disease for a 1-SD lower observational and causal genetically determined BMI. The hazard ratio for a 1-SD lower observational BMI was calculated using Cox regression, whereas the odds ratio for genetically low BMI was derived from the inverse-variance weighted method (upper panel). Estimated effects on Alzheimer's disease risk are plotted against estimated effects on BMI (percent of 1 SD on the log scale) for 32 genetic variants (lower panel). Vertical gray lines show 95% CIs for each individual genetic variant. We graphically illustrated the overall causal estimate shown as a red solid line with 95% CIs as red dashed lines (lower panel). The regression coefficient of –0.021 represents the overall causal estimate. *P* value: significance of hazard ratio or odds ratio.

suggested to be involved in synaptic plasticity, amyloid-β processing, and neuroprotection (35). Because we and others (30, 31) now suggest that BMI is not causally associated with dementia, the proposed biological mechanisms for midlife obesity and Alzheimer's disease are, however, most likely not of a causal nature.

Our study has limitations and strengths that need to be addressed. Although the present analyses do not provide genetic evidence supporting a causal relationship between BMI and Alzheimer's disease, it is not possible based on the present data to entirely negate the hypothesis. The reason for this is that the associations of the genetic variants with BMI are relatively small, and therefore, large numbers of cases and controls are required to reliably preclude any causal relation. However, when comparing the causal genetic estimate from powerful consortia data with the present high-quality observational estimate adjusted for a range of important confounders, the CIs are hardly overlapping, supporting the hypothesis that BMI is not causally associated with Alzheimer's disease. Taken together, the present prospective study and the recent case-control studies (30, 31) provide the first line of evidence arguing against a causal relation between BMI and risk of Alzheimer's disease. A limitation could be the observation that genetically low BMI is associated with low risk of hypertension. This is expected, as a causal relationship exists between high BMI and hypertension (36). However, because genetically low BMI is associated with low risk of hypertension, and because low risk of hypertension is associated with low risk of Alzheimer's disease, these associations cannot explain the present observational relation between low BMI and high risk of Alzheimer's disease. Finally, our study has several strengths, of which the most important are that our findings are based on a large homogenous population, that we control for a number of important confounders, and that we have included as a positive control the well-known causal association between genetically low BMI and low risk of type 2 diabetes.

In conclusion, combining common genetic variation in five key BMI genes into strong genetic instruments and supplementing these analyses with data on Alzheimer's disease risk of 32 BMI variants from international consortia, we found that genetic and hence lifelong low BMI is not associated with high risk of Alzheimer's disease in

the general population. These data suggest that low BMI is not a causal risk factor for Alzheimer's disease, and that the corresponding observational association most likely is explained by reverse causation or confounding.

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