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Original Article

Body Mass Index and Polygenic Risk for Alzheimer's Disease Predict Conversion to Alzheimer's Disease

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Abstract

Body mass index (BMI) is a risk factor for Alzheimer's disease (AD) although the relationship is complex. Obesity in midlife is associated with increased risk for AD, whereas evidence supports both higher and lower BMI increasing risk for AD in late life. This study examined the influence of individual differences in genetic risk for AD to further clarify the relationship between late-life BMI and conversion to AD. Participants included 52 individuals diagnosed as having mild cognitive impairment (MCI) at baseline who converted to AD within 24 months and 52 matched MCI participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. BMI was measured at baseline. Genetic risk for AD was assessed via genome-wide polygenic risk scores. Conditional logistic regression models were run to determine if BMI and polygenic risk predicted conversion to AD. Results showed an interaction between BMI and genetic risk, such that individuals with lower BMI and higher polygenic risk were more likely to convert to AD relative to individuals with higher BMI. These results remained significant after adjusting for cerebrospinal fluid biomarkers of AD. Exploratory sex-stratified analyses revealed this relationship only remained significant in males. These results show that higher genetic risk in the context of lower BMI predicts conversion to AD in the next 24 months, particularly among males. These findings suggest that genetic risk for AD in the context of lower BMI may serve as a prodromal risk factor for future conversion to AD.

Keywords: Genetics, Health factors, Mild cognitive impairment, Neurodegenerative disease, Sex differences

Alzheimer's disease (AD) is a global health concern that is associated with significant memory loss and impaired functioning in everyday life, causing immense costs and burdens to individuals, their families, and health care systems. Approximately 5.8 million Americans are currently living with AD, and the prevalence of AD is expected to increase to 13.8 million by 2050 as the Baby Boomer generation ages (1). AD is characterized by a long preclinical period, whereby neural and biological changes occur prior to noticeable clinical and cognitive symptoms, including neurodegeneration and buildup of tau and β-amyloid peptide (Aβ) (2,3). Approximately 10%–15% of individuals diagnosed with mild cognitive impairment (MCI) progress to AD each year (4). There are no known cures for AD, making it particularly important to investigate risk and protective factors that could be targeted by intervention techniques to prevent conversion to AD.

Health factors, including body mass index (BMI), are thought to play a role in the development of late-onset AD. The relationship between BMI in midlife and risk for dementia is well characterized, such that BMI in the obese range is associated with heightened risk for AD and other types of dementia (5). Obesity is associated with damage to AD-vulnerable regions, such as the hippocampus (6), as well as AD-related pathology, including Aβ and tau (7). The link between obesity and dementia may be, in part, due to inflammation, insulin resistance, oxidative stress, and

metabolic and vascular dysregulation (6,8). Furthermore, genetic variants associated with lower BMI are also associated with higher cognitive abilities (9), which may also contribute to the link between obesity and dementia. However, the relationship between late-life BMI and dementia is less straightforward. Although some work shows that higher BMI is associated with increased risk for progression to AD (10), many studies have demonstrated a *protective* effect of higher BMI against risk for dementia (11,12). Moreover, lower BMI in late life has been associated with increased AD-related pathology in older adults with cognitive impairment (13). Mechanisms that may explain the relationship between lower BMI and AD risk include AD-related damage to brain regions implicated in eating-related behavior and weight regulation, and serotonergic and noradrenergic system abnormalities (14–17). Further complicating the picture, significant relationships between late-life BMI and dementia are not always observed, as evidenced in a meta-analysis by Danat et al. (18).

To better understand the relationship between late-life BMI and late-onset AD, it is important to consider the influence of genetic risk factors; genetics play an integral role in progression to AD and research suggests late-onset AD is highly heritable (60%–80%) (19). However, the majority of previous research has examined BMI and AD genetic risk independently. The small set of studies that have assessed their combined effects have primarily focused on the role of the apolipoprotein E (*APOE*) ε4 allele, demonstrating that in late life, lower BMI among *APOE* ε4 carriers is associated with greater cognitive decline (20) and AD-related pathology (21). *APOE* is certainly the strongest single genetic predictor of AD, accounting for 13% of the phenotypic variance in late-onset AD (22). Nonetheless, polygenic approaches used to measure genetic propensity for AD integrate *APOE* and numerous other genetic variants into a single risk score and can explain more phenotypic variance in AD than single candidate genes (22). Polygenic scores for AD have been independently associated with various neurobiological markers of AD, including cortical thickness (23), hippocampal and entorhinal cortex volume, neurofibrillary tangles, and neuritic plaques (24). Our recent work demonstrated that higher BMI and higher polygenic risk were associated with lower volume in medial temporal lobe regions in older adults with normal cognition (25). One limitation of this previous study was that it was cross-sectional, and thus the direct relationships between BMI, genetic risk, and conversion to AD could not be examined.

The primary goal of this study was to examine the interactive effects of polygenic risk for AD and BMI at baseline in predicting conversion to AD within 24 months using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Additionally, given data showing sex differences in the relationship between BMI and dementia (26) and an interaction between BMI and genetics on AD-related pathology (25), we also implemented exploratory analyses to examine the relationship between BMI, polygenic risk for AD, and progression to AD separately in males and females. Investigating the interactive effects of health and genetic factors longitudinally has implications for developing prevention methods to delay or preclude conversion to AD, as well as clinical utility for identifying individuals at heightened risk for future conversion.

Method

Participants

Data were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2004 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Additional information can be found at www.adni-info.org.

To generate our final sample, we first considered all individuals with available polygenic risk scores (n = 685). Polygenic risk scores were calculated as part of another study for a subset of ADNI participants with available demographic, neuroimaging, and genome-wide genotype data. Moreover, polygenic risk scores were only calculated for participants who identified as White, non-Hispanic/Latino to avoid population stratification effects. Next, we identified participants who also had available demographic data at the baseline and 24-month visits, as well as height and weight data at baseline (n = 520). Next, we identified participants who were diagnosed as early MCI (EMCI) or late MCI (LMCI) at the baseline visit (n = 305). Of these 305 participants, 52 individuals converted to AD within 24 months. The remaining 253 participants were considered for inclusion as matched participants. To generate our matched participants, we first excluded anyone who changed diagnostic categories from baseline to 24 months (n = 25). Next, we used the R function matchControls to select 52 of these 228 individuals to serve as matched participants in the final sample. These participants were specifically matched to individuals who converted to AD based on age, sex, education, and baseline diagnosis. The final sample of 104 older adults aged 55–84 years who were diagnosed with MCI at baseline included 52 individuals who converted to AD within 24 months (referred to as "MCI–AD" for brevity) and 52 matched individuals who did not convert to AD within 24 months (referred to as "MCI–MCI") (see Figure 1).

Exclusion criteria included any neurological disease other than developing or suspected AD, such as, but not limited to, Parkinson's disease, multi-infarct dementia, Huntington's disease, and multiple sclerosis. Moreover, individuals with mental health diagnoses were excluded, including major depression, bipolar disorder, schizophrenia, and alcohol/substance abuse/dependence. Similarly, all participants had to score less than 6 on the Geriatric Depression Scale (Short Form); scores 0–5 are not indicative of depression and scores 6–15 are indicative of depression. Individuals were also excluded if they presented with a history of significant head trauma. To minimize the likelihood of including individuals presenting with dementias other than AD, all participants had to score less than or equal to 4 on the Hachinski Ischemic Scale and show no evidence of infection, infarction, focal lesion, multiple lacunes, or lacunes in memory structures on the baseline MRI scan. Additional details

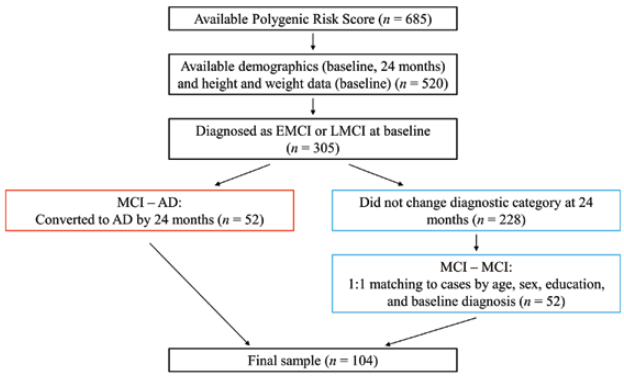

Figure 1. Flow chart detailing generation of the final sample.

about inclusion/exclusion criteria in ADNI can be found in the ADNI protocol (http://adni.loni.usc.edu/methods/documents/).

EMCI, LMCI, and AD were defined according to ADNI's diagnostic criteria, which are described below and can be found in greater detail in the ADNI protocol (http://adni.loni.usc.edu/methods/documents/). EMCI was defined as subjective memory concern, abnormal memory functioning on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A) of the Wechsler Memory Scale—Revised (ie, 9–11 for 16+ years of education, 5–9 for 8–15 years of education, 3–6 for 0–7 years of education), Mini-Mental State Examination (MMSE) score between 24 and 30, Clinical Dementia Rating of 0.5 with the memory box score being at least 0.5, and did not meet criteria for AD. LMCI had the same criteria as EMCI, except the abnormal memory function on the Logical Memory II subscale had to be more severe than the criteria for EMCI (ie, ≤ 8 for 16+ years of education, ≤ 4 for 8–15 years of education, ≤ 2 for 0–7 years of education). AD was defined as subjective memory concern, abnormal memory function on the Logical Memory II subscale (used the same criteria as LMCI), MMSE between 20 and 26, a Clinical Dementia Rating of 0.5 or 1.0, and met NINCSD/ADRDA criteria for probable AD. Study procedures were approved by site-specific Institutional Review Boards and all participants and/or authorized representatives provided written informed consent.

Body Mass Index

Height (inches or centimeters) and weight (pounds or kilograms) were measured at baseline for all participants. Height measurements were converted to meters and weight measurements were converted to kilograms. BMI was calculated using the formula: [weight (kilograms)/height (meters)^2]. There were 25 individuals categorized as normal weight (18.5 ≤ BMI < 25), 56 individuals categorized as overweight (25 ≤ BMI < 30), and 23 individuals categorized as obese (BMI ≥ 30). There were no individuals categorized as underweight (BMI < 18.5).

Polygenic Risk Score Calculation and Genotyping Procedures

We calculated genome-wide polygenic risk scores using beta values to weight all single nucleotide polymorphisms (SNPs) from a genome-wide association study (GWAS), multiplied these weights by the additively coded genotypes (ie, 0, 1, 2), then summed them together to create a single risk score for AD. Our polygenic risk scores integrated all SNPs under a specific p value threshold and were calculated across multiple p value thresholds, as there is no way to predetermine the most predictive threshold. The most predictive score was used for further analyses and was operationalized as the threshold exhibiting the strongest relationship with conversion to AD (described in greater detail below).

The polygenic risk scores for AD in the present study were calculated based on summary statistics from the largest and most recent GWAS on AD, which was conducted on individuals from the International Genomics of Alzheimer's Disease Project (IGAP) who identify as White and non-Hispanic (27). The summary results are available for download at https://www.niagads.org/datasets/ng00075. The risk scores in the present study excluded SNPs with Impute2 quality <0.50 and/or minor allele frequency <0.01. Furthermore, to prevent redundancy, the SNP panel was trimmed for linkage disequilibrium using PLINK's "clumping" procedure prior to imputation (r^2 threshold of .2 in a 500 kb window based on linkage disequilibrium patterns in the 1 000 Genomes EUR sample). Polygenic risk scores were computed across 13 p value thresholds: $p < 1 \times 10^{-8}$, $p < 1 \times 10^{-7}$, $p < 1 \times 10^{-6}$, $p < 1 \times 10^{-5}$, $p < 1 \times 10^{-4}$, $p < 1 \times 10^{-3}$, $p < .01$, $p < .05$, $p < .1$, $p < .2$, $p < .3$, $p < .4$, and $p < .5$.

Genome-wide genotyping was performed using the Illumina HumanOmniExpress BeadChip and processed via GenomeStudio v2011.1 (Illumina). *APOE* was genotyped using DNA from a blood sample. Additional details regarding the genome-wide and *APOE* genotyping procedures used in ADNI are available elsewhere (28).

Cerebrospinal Fluid Biomarkers

Cerebrospinal fluid (CSF) Aβ, total tau, and phosphorylated tau (p-tau) were analyzed at the UPenn/ADNI Biomarker laboratory using the fully automated Roche Elecsys immunoassay (29). The Elecsys Aβ CSF immunoassay in use is not a commercially available in vitro diagnostic assay; it is currently under development and for investigational use only. The measuring range of the assay is 200 (lower technical limit) to 1 700 pg/mL (upper technical limit). The performance of the assay beyond the upper technical limit has not been formally established. Therefore, use of values above the upper technical limit, which are provided based on an extrapolation of the calibration curve, is restricted to exploratory research purposes and is excluded for clinical decision making or for the derivation of medical decision points. In our sample, 14 participants had Aβ values greater than the upper technical limit, which were truncated to 1 700. No participants had values below the lower technical limit for Aβ or outside of the technical limits for tau (80–1 300 pg/mL) or p-tau (8–120 pg/mL).

Statistical Approach

Statistical analyses were performed using R version 3.6.1 for Macintosh. MCI–AD and MCI–MCI participants were compared on relevant demographic and outcome variables using Mann–Whitney U tests for continuous variables, as normality was violated for all variables assessed, and Fisher's exact tests for categorical variables. Baseline BMI and all polygenic risk scores were standardized prior to analyses. To determine the most predictive polygenic risk score threshold to be used in subsequent analyses, conditional logistic regression models were used to examine the effect of genetic risk for AD on conversion to AD within 24 months across all 13 polygenic risk score p value thresholds. We chose the polygenic risk score threshold that showed the strongest relationship (ie, most significant p value) with conversion to AD. The score computed at this threshold was used in all further analyses.

Using hierarchical conditional logistic regression models, our primary analysis was to examine the relationship between BMI and polygenic risk on progression to AD. In the first model, the main effects of BMI and the most significant polygenic score were entered. In the second model, the BMI × polygenic score interaction term was entered. Covariates were not included in the conditional logistic regression models, as MCI–AD and MCI–MCI participants were matched on relevant covariates (age, sex, education, and baseline diagnosis).

Secondarily, we sought to determine if BMI and polygenic risk could explain conversion to AD over and above well-known biomarkers of AD (3). As such, we replicated the BMI × polygenic risk logistic regressions described above including Aβ, tau, and p-tau as covariates. Three participants were missing these CSF biomarkers, which broke MCI–AD/MCI–MCI matching and therefore, unconditional logistic regression models were fit for these analyses. As such, we also included age, sex, education, and baseline diagnosis as covariates. In the first model, age, sex, education, baseline diagnosis,

Aβ, tau, and p-tau were entered. In the second model, polygenic risk and BMI were entered. In the third model, the BMI × polygenic score interaction term was entered. We calculated Nagelkerke's pseudo-R^2 and area under the curve (AUC) as measures of goodness of fit and diagnostic accuracy, respectively, for unconditional logistic regression models; AUC of 0.5–0.7 suggests poor discrimination, 0.7–0.8 suggests acceptable discrimination, and 0.8–0.9 suggests excellent discrimination (30).

We also implemented our primary and secondary analyses described above separately in males and females to examine sex differences in the relationship between BMI, polygenic risk, and conversion to AD. Due to small sample sizes when the overall sample is stratified into males (n = 62) and females (n = 42), these analyses are exploratory and findings should be considered provisional.

To ensure our results were not being driven by outliers, we replicated all analyses after excluding 2 bivariate outliers with respect to BMI and polygenic risk (31); results were similar and therefore the final results do not exclude outliers. We also considered the contribution of cerebrovascular risk factors that are commonly associated with BMI and risk for AD, including smoking, hypertension, diabetes, and hypercholesterolemia/hyperlipidemia. These factors were not significant predictors and are therefore not reported in the final results. Additionally, we implemented correlation analyses to examine the relationship between polygenic risk for AD and cognition at baseline and BMI and cognition at baseline to determine if cognitive functioning may be confounding the observed relationships between BMI, polygenic risk, and conversion to AD. Cognitive status at baseline, as measured via the MMSE, Alzheimer's Disease Assessment Scale 13, and Clinical Dementia Rating sum of boxes, was not associated with polygenic risk for AD or BMI. As such, cognition was not included as a covariate in the final models.

Results

Demographics of the entire sample and as a function of MCI–AD/MCI–MCI status are shown in Table 1. There were no significant differences between the groups in terms of age, sex, education, or baseline diagnosis, indicating that MCI–AD/MCI–MCI matching was successful. There were also no significant differences between MCI–AD and MCI–MCI participants in terms of BMI. There was a significant difference in *APOE* ε4 alleles between MCI–AD and MCI–MCI participants (p = .006). Furthermore, MCI–AD participants had significantly lower CSF Aβ (reflecting greater intracranial Aβ burden) (U = 1 813, p < .001), higher tau (U = 637, p < .001), and higher p-tau (U = 599, p < .001). The conditional logistic regression models indicated the strongest main effect of polygenic risk score at the $p < 1 \times 10^{-6}$ threshold (see Supplementary Table 1 for results at each p value threshold). At this threshold ($p < 1 \times 10^{-6}$), MCI–AD participants had significantly higher polygenic risk for AD than MCI–MCI participants (U = 877, p = .002). The genetic architecture of late-onset AD is yet to be fully elucidated; however, recent work suggests p value thresholds that are more stringent may be indicative of an oligogenic architecture, whereas more lenient p value thresholds may be indicative of a polygenic architecture (32). The optimal polygenic risk threshold here is stringent, which supports the interpretation that the genetic risk of AD reflects an oligogenic architecture.

Table 1. Demographics of the Overall Sample, MCI–AD, and MCI–MCI Participants

	Total[a]	MCI–AD[b]	MCI–MCI[c]	p Value
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	
Age, y	71.8 (7.01)	71.9 (7.42)	71.7 (6.64)	.687
Sex, *N* (%)				
Female	42 (40.4%)	21 (40.4%)	21 (40.4%)	
Male	62 (59.6%)	31 (59.6%)	31 (59.6%)	1
Years of education	16.0 (2.49)	15.9 (2.60)	16.1 (2.39)	.711
Baseline diagnosis, *N* (%)				
EMCI	22 (21.2%)	11 (21.2%)	11 (21.2%)	
LMCI	82 (78.8%)	41 (78.8%)	41 (78.8%)	1
Polygenic risk score[d]	0.00 (1.00)	0.30 (0.97)	−0.30 (0.95)	.002*
BMI[e]	28.0 (5.16)	27.9 (6.14)	28.0 (4.01)	.136
APOE ε4 alleles[f], *N* (%)				
0	46 (44.2%)	15 (28.8%)	31 (59.6%)	
1	41 (39.4%)	26 (50.0%)	15 (28.8%)	
2	17 (16.3%)	11 (21.2%)	6 (11.5%)	.006*
Aβ	915 (424)	749 (305)	1090 (462)	<.001*
Tau	318 (152)	380 (163)	252 (107)	<.001*
P-tau	31.2 (17.4)	38.3 (18.2)	23.6 (12.7)	<.001*

Notes: Aβ = β-amyloid peptide; *APOE* = apolipoprotein E; BMI = body mass index; EMCI = early mild cognitive impairment; LMCI = late mild cognitive impairment; p-tau = phosphorylated tau.

[a]N = 104. [b]N = 52. [c]N = 52. [d]Standardized value. [e]Unstandardized value. [f]Citation: Li et al. (33).

*p < .05.

Overall Sample

Interaction between BMI and polygenic risk score

Hierarchical conditional logistic regression models revealed a significant interaction between BMI and polygenic risk (computed at the $p < 1 \times 10^{-6}$ threshold) in the overall sample (OR = 0.49, 95% CI = 0.25–0.96, p = .036; see Table 2). This interaction can be thought of as indicating that the association between polygenic risk and conversion to AD differed as a function of BMI or conversely that the effect of BMI differed as a function of polygenic risk. To further clarify the interaction between BMI and polygenic risk on conversion to AD, we ran follow-up, unconditional, hierarchical logistic regressions for lower/higher BMI groups (based on median split; unstandardized median = 26.74, standardized median = −0.23). Unconditional logistic regressions were fit since MCI–AD/MCI–MCI matching was broken with the median split. Demographics and statistical comparisons of lower/higher BMI groups are shown in Supplementary Table 2. In the first model, covariates (age, sex, education, and baseline diagnosis) were entered. In the second model, polygenic risk score was entered. Results revealed that among individuals with lower BMI, polygenic risk score significantly predicted conversion to AD (OR = 2.91, 95% CI = 1.51–6.42, p = .003, Nagelkerke's R^2 = .31, AUC = 0.78). Among individuals with higher BMI, polygenic risk did not significantly predict conversion to AD (OR = 1.27, 95% CI = 0.69–2.39, p = .451, Nagelkerke's R^2 = .07, AUC = 0.63).

CSF biomarker analyses

We next conducted hierarchical unconditional logistic regressions with CSF biomarkers to determine if BMI and polygenic risk could predict conversion to AD after adjusting for core biomarkers of AD. Age, sex, education, baseline diagnosis, Aβ, tau, and p-tau significantly predicted conversion to AD with excellent diagnostic accuracy [χ^2 (7, N = 101) = 33.31, p < .001, Nagelkerke's R^2 = .41, AUC = 0.80]. Adding polygenic risk and BMI in model 2 [$\Delta\chi^2$ (2, N = 101) = 2.37, p = .306, Nagelkerke's R^2 = .43, AUC = 0.81]

Table 2. Summary of Conditional Logistic Regression Analysis for Association With Conversion to AD in the Overall Sample

	Model 1			Model 2		
Variable	Adjusted OR	95% CI	*p* Value	Adjusted OR	95% CI	*p* Value
BMI	1.06	0.70–1.62	.769	1.02	0.66–1.57	.928
PRS	1.77	1.15–2.71	.009**	1.78	1.11–2.84	.016*
BMI × PRS				0.49	0.25–0.96	.036*
Model LRT	8.21*			13.31**		

Notes: BMI = body mass index; LRT = likelihood ratio test; PRS = polygenic risk score. BMI and PRS were standardized prior to analyses.
*$p < .05$. **$p < .01$.

did not significantly improve the overall model. Adding the BMI × polygenic risk interaction in model 3 significantly improved the overall model [$\Delta\chi^2$ (1, N = 101) = 5.48, p = .019, Nagelkerke's R^2 = .48, AUC = 0.83].

Sex-Stratified Samples

Interaction between BMI and polygenic risk score

Sex differences in the relationship between BMI and polygenic risk on conversion to AD were explored next. Demographics and statistical comparisons of males and females are shown in Supplementary Table 3. Among males, there was a significant interaction between BMI and polygenic risk on conversion to AD (OR = 0.28, 95% CI = 0.09–0.85, p = .025; see Supplementary Table 4). Among females, there was no significant interaction between BMI and polygenic risk (OR = 1.18, 95% CI = 0.28–4.97, p = .821) or main effect of BMI (OR = 1.17, 95% CI = 0.59–2.30, p = .649); however, there was a main effect of polygenic score on conversion to AD (OR = 2.52, 95% CI = 1.07–5.93, p = .034; see Supplementary Table 5).

To further clarify the interaction between BMI and polygenic risk score on progression to AD in males, we ran follow-up, unconditional, hierarchical logistic regressions for lower/higher BMI groups (based on median split; unstandardized median = 27.57, standardized median = −0.07), as described above for the overall sample. Results revealed that among males with lower BMI, polygenic risk score significantly predicted conversion to AD (OR = 2.99, 95% CI = 1.32–8.31, p = .017, Nagelkerke's R^2 = .37, AUC = 0.81). Among males with higher BMI, polygenic risk did not significantly predict conversion to AD (OR = 0.95, 95% CI = 0.42–2.09, p = .905, Nagelkerke's R^2 = .04, AUC = 0.59).

CSF biomarker analyses

Hierarchical unconditional logistic regressions revealed the sex-stratified results remained significant after adjusting for Aβ, tau, and p-tau. In males, age, education, baseline diagnosis, Aβ, tau, and p-tau predicted conversion to AD with excellent diagnostic accuracy [χ^2 (6, N = 61) = 22.12, p = .001, Nagelkerke's R^2 = .42, AUC = 0.81]. Adding polygenic risk and BMI in model 2 [$\Delta\chi^2$ (2, N = 61) = 2.74, p = .255, Nagelkerke's R^2 = .46, AUC = 0.83] did not significantly improve the overall model. Adding the BMI × polygenic risk interaction in model 3 significantly improved the overall model [$\Delta\chi^2$ (1, N = 61) = 10.59, p = .001, Nagelkerke's R^2 = .60, AUC = 0.89]. In females, age, education, baseline diagnosis, Aβ, tau, and p-tau predicted conversion to AD with excellent diagnostic accuracy [χ^2 (6, N = 40) = 16.25, p = .012, Nagelkerke's R^2 = .50, AUC = 0.87]. Adding polygenic risk and BMI in model 2 [$\Delta\chi^2$ (2, N = 41) = 1.70, p = .427, Nagelkerke's R^2 = .53, AUC = 0.85] and the BMI × polygenic risk interaction in model 3 [$\Delta\chi^2$ (1, N = 41) = 0.11, p = .740, Nagelkerke's R^2 = .53, AUC = 0.87] did not significantly improve the overall model.

Discussion

This study examined the relationship between BMI, polygenic risk for AD, and conversion to AD within 24 months. There were 2 primary findings. First, the interaction between BMI and polygenic risk predicted conversion to AD, such that lower BMI and higher polygenic risk increased likelihood of conversion, whereas there was no association between polygenic risk and conversion among individuals with higher BMI; this finding remained significant even after adjusting for the effects of Aβ, tau, and p-tau. Second, exploratory analyses revealed that the relationship between BMI, polygenic risk, and conversion to AD was more pronounced in males.

The results presented here show that 24 months prior to an AD diagnosis, lower BMI, in combination with greater genetic risk for AD, is associated with conversion to AD. Genetic risk for AD is associated with alterations and atrophy in various brain regions, including the amygdala, hippocampus, and other medial temporal regions (24,34–36), as well as differential gene expression in regions implicated in AD, such as temporal regions (37). Inflammation and oxidative stress are 2 specific pathways that genetic risk for AD likely acts through to facilitate neurodegeneration (38–40). One interpretation of our results is that lower BMI acts through, and exacerbates, these genetic pathways. It is often proposed that lower BMI in the 10 years preceding an AD diagnosis is a consequence of AD pathology (41); AD pathology may induce damage to brain regions that are implicated in eating-related behavior and weight regulation, such as the amygdala, hypothalamus, cingulate gyrus, hippocampus, and other medial temporal regions (14–17), leading to body weight loss and consequently lower BMI. AD pathology may specifically induce damage to these regions through oxidative stress and inflammation (38,40). This suggests that higher genetic risk for AD and AD-related damage contributing to lower BMI may affect the same neural pathways; therefore, these 2 risk factors in combination may lead to greater neurobiological disruptions and consequently increase the risk of clinical manifestation of AD. Nevertheless, additional work is needed to elucidate the specific, synergistic mechanisms underlying this interaction. One specific factor that warrants consideration and should be further investigated is the role of sarcopenia (ie, losing muscle mass and function). Sarcopenia is associated with lower BMI (42) and may be caused by AD-related pathology, including oxidative stress and inflammation (43), both of which are also genetic pathways of AD (39). Thus, sarcopenia may mediate the relationship between BMI, genetic risk for AD, and conversion to AD. Another factor

that warrants consideration is frailty, which is characterized, in part, by weight loss (44) and is associated with increased risk for dementia (45), including AD (46). Furthermore, frailty is associated with inflammation (47) and oxidative stress (48), further demonstrating that it may contribute to the observed relationship between BMI, genetic risk for AD, and conversion to AD. A second interpretation of these findings that warrants consideration is that there is a protective effect of maintaining higher BMI that may help to counteract the negative pathways of genetic risk for AD. Specifically, leptin is a hormone produced by adipose tissue that has neuroprotective properties, including hippocampal synaptic plasticity and corresponding learning and memory outcomes (49). As such, the neuroprotective effects of leptin, specifically in regions vulnerable to AD such as the hippocampus, may offset some of the negative effects of genetic risk for AD in these regions to preclude conversion to AD. Although, to further explore this interpretation, future work should examine how leptin interacts with genetic risk for AD to influence progression to AD.

Findings of this study also showed that the interaction between BMI and polygenic risk for AD remained significant after adjusting for Aβ, tau, and p-tau, which are some of the most well-known biomarkers of AD (3). These results underscore the importance of considering health and genetic factors as well as their synergistic effects when examining risk for late-onset AD, as they have predictive power beyond common AD biomarkers and can help us characterize this multifactorial disease better than any factor can in isolation. Nonetheless, it is important to acknowledge that the effect of BMI and genetic factors is relatively small after accounting for the most predictive biomarkers of AD.

Our exploratory analyses indicated that the relationship between BMI and polygenic risk on conversion to AD was stronger in male participants. This finding was initially surprising, as females are at greater risk for AD (50) and previous research suggests that the relationship between BMI and dementia (26), as well as BMI, genetics, and AD-related pathology (25), may be stronger in females. A potential explanation for the sex differences observed in this study considers the role of testosterone, which decreases throughout the aging process, specifically among males (51,52), and has been associated with lower BMI in older males (53). Low testosterone is consistently identified as a risk factor for AD (53), specifically during the preclinical phase (54), and interacts with *APOE* ε4 to confer risk for AD (52). Decreased testosterone and genetics may specifically interact and increase risk for late-onset AD via inflammatory pathways (38,51), although additional work is needed to clarify the role of testosterone in the relationship between BMI and genetic risk for AD on AD risk, specifically among males. Furthermore, due to small sample sizes, these findings should be considered provisional and should be replicated with larger sample sizes.

This study has several limitations. First, while it is beneficial that this study was able to examine BMI, genetics, and progression to AD longitudinally, ADNI does not collect data on BMI prior to the baseline assessment. As such, the relationship between lifetime BMI, genetic risk, and late-onset AD could not be examined. Furthermore, it would be useful to examine the relationship between late-life BMI and progression to AD over a longer period of time. However, attrition in ADNI increases at later timepoints; we chose to preserve power and minimize non-random dropout that may bias results, which consequently sacrificed the ability to examine this relationship over a longer timeframe (ie, 4–5 years). Additional work is needed to examine the relationship between BMI at various points across the life span, genetic risk for AD, and AD, including earlier in the disease process as some of the neurobiological changes of AD begin to develop. Similarly, future work should also examine the interplay between BMI and polygenic risk on the progression from cognitively normal to MCI. While we selected the timeframe of this study to maximize power, our sample is still relatively small and is therefore another limitation of the current study. Until this study can be replicated with additional, larger sample sizes, the findings should be considered provisional. Risk for AD is also influenced by various lifestyle factors, such as physical activity, diet, mental stimulation, and social engagement (55). These variables were not assessed in ADNI and therefore we could not determine how these factors may contribute to conversion in the present study, which is another limitation of this study. Similarly, ADNI does not collect data on midlife and therefore the influence of various vascular and lifestyle factors in midlife on conversion to AD in late life could not be examined. Another limitation of this study is that our sample did not include any individuals categorized as underweight. Underweight BMI, genetic risk, and progression to AD should be examined, as there is evidence that late-life, underweight BMI may increase dementia risk (56). Finally, our sample only included older adults who identify as White, non-Hispanic/Latino and additional work is needed to clarify how BMI and genetic risk interact to influence progression to AD in other racial and ethnic groups.

In conclusion, this study showed that polygenic risk for AD had a greater impact on risk in those with lower BMI on the likelihood of conversion to AD within 24 months, specifically among males. No association was observed between polygenic risk and AD in individuals with higher BMI. This interaction remained significant even after adjusting for Aβ, tau, and p-tau, the core biomarkers of AD. These results suggest that genetic risk for AD in the context of lower BMI may serve as a predictor of future progression to AD. Moreover, these results may help clinicians identify individuals at heightened risk of developing late-onset AD who should be monitored more closely for pathological decline and may benefit most from interventions attempting to delay or prevent progression to AD. This study underscores the importance of examining the synergistic effects of health and genetic risk factors to better characterize late-onset AD, which may be used to inform prevention methods.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

J.N.M. designed and conceptualized the study, analyzed and interpreted the data, and drafted the manuscript. K.E.V. analyzed and interpreted the data and critically revised the manuscript for intellectual content. A.N.H. analyzed the data and critically revised the manuscript for intellectual content. S.P. interpreted the data and critically revised the manuscript for intellectual content. M.W.L. analyzed and interpreted the data and critically revised the manuscript for intellectual content. S.M.H. conceptualized the study and critically revised the manuscript for intellectual content. J.P.H. designed and conceptualized the study, interpreted the data, and critically revised the manuscript for intellectual content. All authors approve of the final manuscript and agree to be accountable for all aspects of the work.

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