BMC Public Health

RESEARCH

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The association between BMI and cognition in India: data from the Longitudinal Aging Study in India (LASI)

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Abstract

Background High body-mass index (BMI) is an established risk factor for late-life cognitive impairment and dementia, but most evidence comes from high-income contexts. Existing evidence from cross-sectional data in low- and middle-income settings is inconsistent, and many studies do not adequately address potential sources of bias.

Methods We used data from Wave 1 of the Longitudinal Aging Study in India (LASI) (analytic $N = 56{,}753$) to estimate the association between BMI categories and cognitive functioning among older adults aged 45 + years using survey-weighted linear regression models stratified by gender and controlling for potential confounders including demographic factors, socio-economic status (SES) characteristics, and health-related behaviors. To probe potential sources of bias, including residual confounding and reverse causation, we used weighting and trimming methods, sample restriction, and explored effect modification.

Results In fully adjusted models, relative to normal BMI underweight BMI was associated with lower cognitive scores (Men: -0.16 SD difference, 95% CI -0.18, -0.13; Women: -0.12 SD, -0.15, -0.10). Overweight and obesity were associated with higher cognitive scores in both men (overweight: 0.09; 0.07, 0.12, obese: 0.10; 0.05, 0.15) and women (overweight: 0.09; 0.07–0.12, obese: 0.12; 0.08–0.15). Estimates were similar after weighting and trimming but were attenuated after excluding those with low cognition (≥1 SD below the mean relative to those with similar demographic characteristics). Positive associations between overweight and obese BMI and cognition were attenuated or null in those living in urban settings and those with higher levels of educational attainment.

Conclusions Underweight BMI is a risk factor for poor cognitive outcomes in adults 45 years and older and may be indicative of poor nutritional status and life-course disadvantage in India. In tandem with existing literature, supplemental analyses and effect modification results indicate that unmeasured confounding and reverse causation may explain the observed positive associations between overweight and obese BMI and cognitive functioning from cross-sectional studies in low- and middle-income settings. Future data with longitudinal follow-up will be helpful to further disentangle biases.

Keywords Cognition, Body mass index, Obesity, India

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Introduction

Midlife body-mass index (BMI) is a well-established risk factor for dementia [1, 2]. However, most studies linking BMI and cognitive health come from high-income contexts [3–5]. Given that 68% of individuals with dementia are expected to live in low- and middle-income countries by 2050 [6], understanding differences between high-income and low- or middle-income contexts is important.

The population of older adults (>60 years of age) in India is the second-largest globally, and is expected to more than double by 2050 [7]. The number of individuals with dementia in India is also expected to almost double by 2050 [8]. In India and other developing countries, demographic and epidemiologic transitions have led to increases in the proportion of individuals who are overweight and obese, while the proportion of the population with underweight BMI remains high [9–11].

Studies on the association between BMI and cognitive outcomes from low- and middle-income settings have had mixed results. While some have reported that overweight and obese BMI are associated with higher risk of cognitive impairment [12, 13], many others have reported null or opposite findings [14–17]. Three prior studies in India found that those who were underweight had worse cognition, while those who were overweight or obese had higher levels of cognition compared to individuals in the normal BMI range [18–20]. However, existing cross-sectional studies have largely ignored important analytic issues that can lead to biases.

Several methodological challenges must be carefully considered and evaluated when studying the association between BMI and cognitive outcomes using cross-sectional data from in low- and middle-income settings. First, in low- and middle-income settings, factors that are largely considered beneficial for health, such as income level and socio-economic status (SES), are associated with factors largely considered harmful to health, such as access to processed foods and increased intake of foods with high fat levels and added sugar [9, 21, 22]. These patterns create strong confounding structures, which may not be appropriately addressed through traditional observational research methods. Second, evidence that declining BMI is associated with worse cognitive outcomes and declining cognition at later time points raises concern that cross-sectional findings of positive associations between BMI and cognition may be explained by reverse causation [23, 24].

Using data from the Longitudinal Aging Study in India (LASI), we sought to improve on existing cross-sectional studies in low- and middle-income contexts by carefully considering and characterizing potential biases. We implement several methods for controlling for confounding beyond traditional regression adjustment, assess effect modification by factors that may influence sources of bias, and conduct a wide array of sensitivity analyses to provide a more comprehensive understanding of observed associations.

Materials and methods

Sample

The Longitudinal Aging Study in India (LASI) is a nationally representative survey of over 72,000 adults aged 45 years and older and their spouses in India [25]. Wave 1 of the survey was fielded between 2017–2019 and collected data included demographics, self-reported health conditions, physical measurements and biomarkers, and measures of cognitive functioning. The study was approved by the relevant Institutional Review Boards and informed consent was obtained from participants. For this analysis, we excluded individuals under 45 ($N=6{,}687$), individuals with missing BMI ($N=6{,}504$), missing cognitive score ($N=2$), or missing information on other covariates ($N=2{,}316$) (Appendix Fig. S1) ($N=56{,}753$). However, we also conducted multiple imputation to assess the robustness of our main findings to these exclusions in a sensitivity analysis (sensitivity analysis $N=65{,}575$).

Measurement of BMI and waist circumference

Measured height and weight were used to calculate BMI. We used proposed South Asian BMI cutoffs (<18/18–22.9/23–25/>25 kg/m^2) [26] in primary analyses and WHO BMI cutoffs (<18.5/18.5–24.9/25–29.9/>30 kg/m^2) [27] in sensitivity analyses. Waist circumference was measured to the nearest tenth of a centimeter and was used both continuously and categorized into quartiles for analysis.

Measurement of cognition

We used a general cognitive factor score estimated from 22 cognitive tests administered. Tests covered cognitive domains including orientation to time and place, immediate and delayed memory, executive functioning, language, and visuospatial functioning (full list in Appendix). We estimated the latent trait using a graded response item response theory model [28], which captures the common covariance between cognitive test items as a way of quantifying the underlying latent trait.

To improve the performance of this model, we incorporated more intensive cognitive testing from the LASI Diagnostic Assessment of Dementia (LASI-DAD) substudy ($N=4{,}096$) [29]. We included all 11 common and 42 non-common items in both the LASI and LASI-DAD studies in the item-response theory model. We scaled the general factor score to have a mean of 0 and variance

of 1 within the LASI-DAD population; in the current sample the mean and standard deviation were -0.01 and 0.98 (men: 0.30 [SD = 0.97], women: -0.29 [SD = 0.97]). Ninety-seven percent of estimated scores had marginal reliabilities above 70% and scores were not sensitive to the inclusion of items that were dependent on literacy (correlation between scores including and excluding these items was 0.995).

Assessment of covariates

Covariates included state of residence, rural/urban residence, self-reported age, gender, marital status (married or partnered/not married or partnered), literacy status (reported ability to read or write), education (no school/less than secondary school/secondary or higher secondary school/graduate school) and caste (no caste or other caste, scheduled caste, scheduled tribe, other backwards class). We considered health-related behaviors, including smoking status (ever/never smoked or used smokeless tobacco), and self-reported moderate and vigorous physical activity (everyday/more than once per week/once per week/1–3 times per month/hardly ever or never). We also considered covariates capturing socioeconomic status, including parental education (same categorization as above), per capita consumption quintile, and housing material (permanent vs. non-permanent materials). Finally, we considered depression symptomology assessed using the short form of the Composite Diagnostic Interview (CIDI-SF) [30]. We categorized the total number of symptoms into three categories (No symptoms, 1–3 symptoms, 4–7 symptoms) based on the distribution of the data.

Statistical methods

We used descriptive statistics (means, proportions) to compare covariates and cognitive scores across BMI categories. To conduct statistical comparisons across BMI categories we used t-tests, 1-way ANOVA tests, and chi-squared tests.

We used linear regression to estimate associations between BMI category and cognitive score. Prior research and initial models suggested the presence of an interaction between gender and BMI [31]. In subsequent models including interactions between BMI and all covariates, we observed significant interactions between gender and 7 of 14 hypothesized confounders. Because results suggested complex interrelationships between gender, cognition, and BMI as well as the hypothesized confounding structures, we stratified all subsequent analyses by gender. Although prior research has shown evidence of effect modification by age in the association between BMI and cognition [31, 32], in this setting effect modification by age category (< 50/51–60/61–70/71–80/81 +) was not statistically significant for men ($p = 0.339$) or women ($p = 0.562$). Therefore, subsequent models did not consider interactions by age category.

We estimated three sets of models considering a range of factors hypothesized to be confounders of the association between BMI and cognition: Model 1 did not adjust for confounders, Model 2 adjusted for demographic factors (age [estimated with a natural cubic spline with internal knots at the 33rd and 66th percentiles and external knots at the 5th and 95th percentiles], and educational attainment), and Model 3 additionally adjusted for all other potential confounders considered (described earlier). To contextualize findings, we compared the magnitude of coefficients to the coefficient for age from a model with only age (linear) and gender. As an alternative to using BMI categories, we also estimated an alternative version of Model 3 using a natural cubic spline on BMI with internal knots at the 33rd and 66th percentiles and external knots at the 5th and 95th percentiles to capture nonlinearities in the association between BMI and cognition. We estimated E-values to quantify the strength of unmeasured confounding necessary to explain observed effect sizes [33].

We conducted follow-up analyses to address potential residual and unmeasured confounding, or reverse causation. First, we used two weighting approaches for controlling for confounding: inverse probability of treatment weighting and overlap weighting (details in Appendix) [34]. Overlap weights are derived from the same propensity scores used in inverse probability of treatment weighting, but down-weight individuals with extreme propensity scores and therefore make the two exposure groups more comparable. Second, we used trimming in addition to weighting to refine the target population and limit analyses to a study population with greater exchangeability between exposure groups, which has been shown to reduce unmeasured confounding in simulation studies [35]. For all models with weighting, we estimated models with and without controlling for all confounders included in Model 3. We also re-estimated models excluding those with low cognition (≥1 SD below the mean relative to those with similar demographic characteristics), as those with low cognition may drive reverse causation findings (details in Appendix).

Older adults with greater levels of education or who live in urban areas may have greater cognitive reserve and therefore, may be more resilient to early cognitive decline [36]. Thus, if reverse causation due to early cognitive decline were responsible for positive associations between higher BMI and higher cognition, we would expect attenuated associations in these groups. Additionally, if those with greater education or those living in urban areas are more homogenous, there may be

less variability in demographic or SES-related factors, and therefore less residual and unmeasured confounding within these subpopulations. We examined results across strata defined by rural/urban residence and educational attainment to assess the potential impact of these hypothesized biases. We used linear combinations of coefficients from regression models (adjusted for covariates in Model 3) with interaction terms to quantify stratified associations. We used chi-square tests to compare the overall statistical significance of adding the interaction terms.

In a sensitivity analysis, we used multiple imputation to fill in missing data on BMI, cognition, and covariates and re-estimated regressions to evaluate the effect of using complete case analysis. Additionally, we explored the use of WHO BMI cutoffs rather than those specific to Asian Indians [26], and use of waist circumference as an alternative measure of adiposity. All analyses used survey weights to account for the complex survey design. Item response theory models were estimated in Mplus Version 8. All other analyses were done using R version 4.2.2.

Results

Of 56,753 participants included in main analyses, 16.6% (95% Confidence Interval [CI] 16.2–17.0) were underweight, 42.0% (41.5–42.6) were normal weight, 14.6% (14.3–15.0) were overweight, and 26.7% (26.3–27.2) were obese. Markers of SES were strongly associated with BMI categories (Table 1). Individuals who were overweight and obese were more highly educated, more likely to be literate, less likely to belong to a scheduled caste or tribe, more likely to have housing built from permanent materials, and had higher per capita consumption. The opposite was true of those in the underweight category. Those in the overweight and obese categories were less likely to smoke but also less likely report moderate or vigorous physical activity. All statistical tests of differences were statistically significant ($p < 0.001$).

In both men and women, cognitive scores were lowest in underweight individuals, followed by individuals with normal BMI, overweight BMI, and then obese BMI (Table 1; Fig. 1). Crude patterns were attenuated but still present in models adjusting for demographic variables and for all considered confounders. In fully adjusted models, relative to normal BMI, underweight BMI was associated with a -0.13 (95% CI -0.16- -0.10) SD lower cognitive score in men and a -0.11 (-0.14- -0.10) SD lower cognitive score in women (Table 2, Appendix Table S1). Overweight and Obese BMI were associated with higher cognitive scores in both men (overweight: 0.11;0.08–0.14, obese: 0.14;0.11–0.16) and women (overweight: 0.07;0.04–0.10, obese: 0.13;0.10–0.15). As the estimated coefficient for age was -0.03 SD per year of age, observed associations were equivalent to between 2–4 years of age, suggesting observed effect sizes are small to moderate. Findings were consistent in models using splines to capture nonlinearities in the association between BMI and cognition; in both men and women predictions of cognition increased linearly over BMI before flattening out at a BMI of 25 kg/m^2, the threshold for obesity according to the South Asian cutoffs (Fig. 2). Across fully adjusted models for men and women, E-values ranged from 1.34 to 1.52 (Appendix Table S2). Estimates indicate, for example, that to explain the observed association between obesity and cognition, a set of unobserved confounders would have to be associated with both obesity and cognition with a relative risk of 1.52 and 1.49 in men and women, respectively [37].

Inverse probability weights and overlap weights effectively balanced included confounders (Appendix Fig. S2). Distributions of propensity scores had some areas of non-overlap prior to trimming, indicating potential lack of exchangeability between exposure groups. After trimming, there were no sections of the distribution without overlap (Appendix Figures S3, 4). However, estimates for associations did not change substantially after applying weighting and trimming methods (Fig. 3). For all additional estimates considered (48), estimated confidence intervals always included the corresponding mean estimate from Model 3. After excluding those with low cognition, estimates were attenuated but remained statistically significant (Appendix Fig. S5).

We observed effect modification of the association between cognition and BMI category by educational attainment and rural/urban residence (Fig. 4). Chi-squared tests indicated significant effect modification among men for rural/urban residence ($p = 0.027$) and educational attainment ($p = 0.027$), but not among women (rural/urban $p = 0.082$; educational attainment $p = 0.169$), though patterns of findings were similar across genders. Estimates of associations between overweight and obesity were smaller or null in sub-groups with higher educational attainment or those in urban settings; estimates were shifted further in results from models excluding those with low cognition (Appendix Figure S6).

Sensitivity analyses using alternative WHO BMI cutoffs (Appendix Figure S7), using waist circumference quartile instead of BMI category (Appendix Figure S8 & S9), or using multiply imputed data (Appendix Figure S10) yielded similar findings.

Discussion

In this study, underweight BMI was associated with lower cognitive scores and both overweight and obese BMI were associated with higher cognitive scores. The association was approximately linear over most of the

Table 1 Characteristics of participants in theLlongitudinal Aging Study in India (LASI) included in main analyses ($N = 56,753$)

	All	Underweight	Normal	Overweight	Obese
N	56,753	8471	23,227	8571	16,484
Age	58.7 (50.0—65.0)	61.9 (53.0—70.0)	58.9 (50.0—65.0)	57.6 (50.0—64.0)	57.0 (50.0—63.0)
45–49	25.9 (14,301)	18.5 (1465)	25.9 (5624)	28.8 (2333)	28.9 (4879)
50–59	36.1 (18,350)	30.5 (2273)	35.4 (7303)	37.8 (2928)	39.8 (5846)
60–69	25.5 (15,723)	30.4 (2734)	25.4 (6543)	23.7 (2249)	23.5 (4197)
70–79	9.7 (6519)	15.0 (1460)	10.3 (2901)	8.0 (871)	6.5 (1287)
80+	2.8 (1860)	5.5 (539)	3.0 (856)	1.7 (190)	1.3 (275)
Women	46.5 (30,322)	45.6 (4424)	41.9 (11,282)	45.1 (4411)	55.0 (10,205)
Cognition	-0.02 (-0.71—0.68)	-0.50 (-1.12—0.13)	-0.12 (-0.78—0.54)	0.18 (-0.49—0.84)	0.32 (-0.32—0.98)
Rural	68.9 (37,361)	86.1 (7170)	76.8 (17,240)	62.4 (5178)	49.5 (7773)
Education					
No school	52.6 (26,797)	70.3 (5646)	58.0 (12,243)	44.8 (3382)	37.5 (5526)
Less than secondary school	21.5 (14,024)	18.5 (1830)	21.1 (5761)	23.0 (2243)	23.2 (4190)
Secondary and higher secondary	20.8 (13,118)	10.2 (914)	17.4 (4475)	25.4 (2361)	30.2 (5368)
Graduate school	5.0 (2814)	1.0 (81)	3.5 (748)	6.8 (585)	9.1 (1400)
Per Capita Consumption					
Quintile 1	22.4 (11,609)	32.8 (2764)	26.3 (5663)	17.3 (1364)	12.5 (1818)
Quintile 2	21.7 (11,615)	25.8 (2111)	23.0 (5179)	21.3 (1660)	17.2 (2665)
Quintile 3	20.0 (11,345)	18.9 (1604)	20.0 (4742)	20.4 (1738)	20.4 (3261)
Quintile 4	18.8 (11,135)	13.9 (1192)	17.0 (4143)	20.8 (1884)	23.6 (3916)
Quintile 5	17.2 (11,049)	8.5 (800)	13.7 (3500)	20.2 (1925)	26.5 (4824)
Caste					
No caste or other caste	26.4 (15,418)	17.6 (1535)	23.0 (5314)	29.2 (2570)	35.7 (5999)
Other backward class	44.9 (21,589)	42.1 (3246)	44.9 (8742)	46.8 (3262)	45.6 (6339)
Scheduled caste	20.0 (9662)	25.6 (1837)	21.6 (4210)	17.8 (1314)	15.1 (2301)
Scheduled tribe	8.7 (10,084)	14.7 (1853)	10.4 (4961)	6.2 (1425)	3.6 (1845)
Permanent house material	54.1 (30,407)	35.2 (2942)	48.4 (10,748)	61.3 (5163)	70.9 (11,554)
Literate	46.7 (29,195)	28.7 (2658)	41.1 (10,613)	54.9 (5102)	62.2 (10,822)
Paternal Education					
No school	74.1 (41,309)	85.3 (7175)	78.3 (17,973)	69.4 (5878)	63.1 (10,283)
Less than secondary school	15.9 (9704)	10.7 (959)	14.3 (3573)	18.4 (1703)	20.3 (3469)
Secondary and higher secondary	8.7 (5010)	3.8 (313)	6.6 (1516)	10.6 (862)	13.9 (2319)
Graduate school	1.3 (730)	0.3 (24)	0.9 (165)	1.7 (128)	2.6 (413)
Depression symptoms					
No symptoms	90.8 (52,391)	88.4 (7630)	90.9 (21,458)	91.2 (7947)	91.9 (15,356)
1–3 symptoms	2.4 (1191)	2.8 (206)	2.2 (458)	2.6 (197)	2.3 (330)
4–7 symptoms	6.8 (3171)	8.7 (635)	6.9 (1311)	6.2 (427)	5.8 (798)
Moderate physical activity					
Hardly ever/never	30.1 (17,193)	32.0 (2721)	28.7 (6907)	30.7 (2636)	30.7 (4929)
1–3 times/month	3.6 (1714)	4.1 (292)	3.7 (726)	3.6 (258)	3.0 (438)
Once/week	3.9 (2172)	3.5 (298)	4.2 (934)	4.1 (330)	3.6 (610)
More than once/week	6.4 (3775)	6.6 (559)	6.4 (1624)	6.1 (579)	6.2 (1013)
Everyday	56.1 (31,899)	53.8 (4601)	57.0 (13,036)	55.5 (4768)	56.5 (9494)
Vigorous physical activity					
Hardly ever/never	55.6 (33,729)	55.7 (4941)	51.1 (12,763)	56.5 (5168)	62.3 (10,857)
1–3 times/month	5.4 (2897)	5.3 (458)	5.8 (1241)	5.5 (436)	4.9 (762)
Once/week	3.8 (2117)	3.9 (340)	4.3 (908)	3.1 (277)	3.5 (592)
More than once/week	7.5 (4068)	8.7 (677)	8.2 (1896)	7.7 (632)	5.5 (863)
Everyday	27.6 (13,942)	26.4 (2055)	30.7 (6419)	27.2 (2058)	23.8 (3410)
Ever smoked	20.2 (10,519)	29.7 (2345)	23.0 (4997)	17.3 (1402)	11.4 (1775)

Survey weighted means and inter-quartile ranges are shown for continuous variables, and survey weighted means and unweighted numbers are shown for binary variables

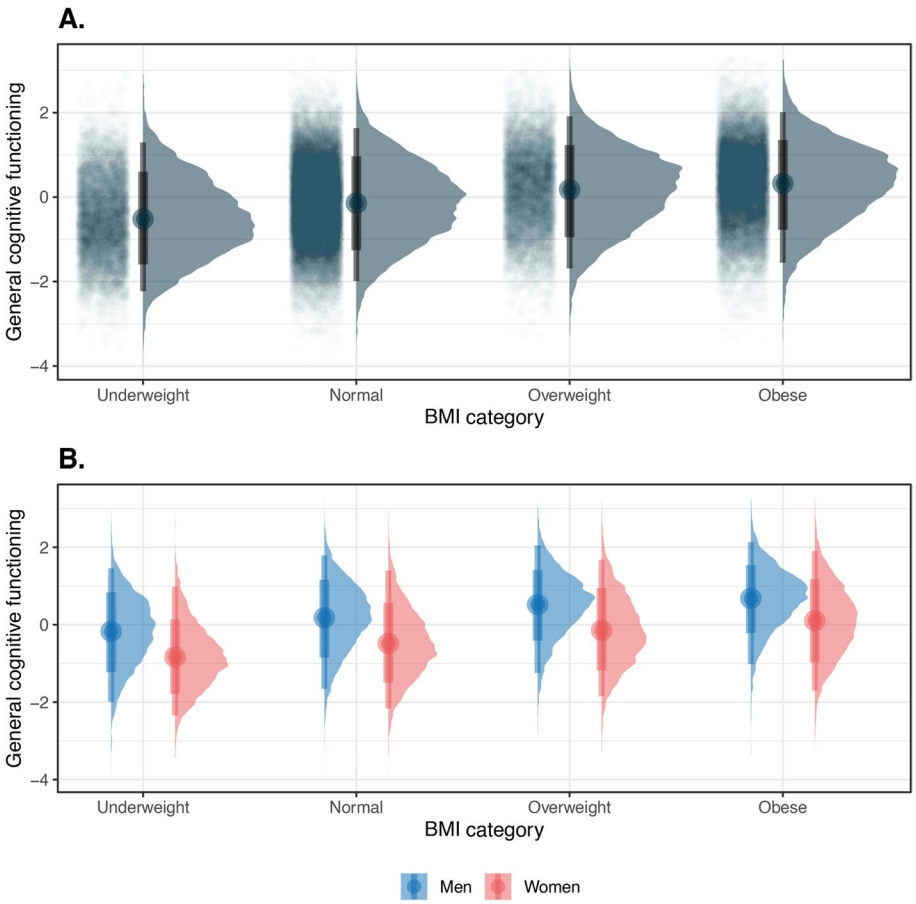

Fig. 1 Distributions of cognitive scores by body-mass index (BMI) category for participants in the Longitudinal Aging Study in India ($N = 56{,}753$)

Table 2 Associations between BMI category and cognition by gender from linear regression models

	Underweight	Overweight	Obese
Men			
Crude	-0.36 (-0.40—-0.32)***	0.34 (0.30—0.38)***	0.51 (0.48—0.54)***
Adjusted for demographics	-0.17 (-0.20—-0.14)***	0.15 (0.12—0.18)***	0.19 (0.17—0.22)***
Fully adjusted	-0.13 (-0.16—-0.10)***	0.11 (0.08—0.14)***	0.14 (0.11—0.16)***
Women			
Crude	-0.32 (-0.36—-0.29)***	0.30 (0.26—0.34)***	0.56 (0.53—0.59)***
Adjusted for demographics	-0.17 (-0.20—-0.14)***	0.12 (0.09—0.15)***	0.21 (0.19—0.23)***
Fully adjusted	-0.11 (-0.14—-0.08)***	0.07 (0.04—0.10)***	0.13 (0.10—0.15)***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, Models adjusting for demographic variables adjusted for continuous age (spline), and educational attainment. The full adjustment set additionally included state, rural/urban residence, marital status, literacy, caste, paternal education, per capita consumption quintile, housing materials, smoking status, depressive symptoms, and moderate and vigorous physical activity. Coefficients can be interpreted as differences in SD units of cognition comparing each BMI category to individuals in the normal BMI group

range of BMI but flattened out at a BMI of 25 kg/m^2. Results were consistent across analyses attempting to further control for residual and unobserved confounding but were attenuated in models excluding those with low cognition and in subgroups with higher education and in urban settings.

Results of cross-sectional associations between BMI category and cognition are in line with other studies from low- and middle-income settings including Chile [12], China [38], Central African Republic and Republic of Congo [39], South Africa [40], and India [20]. While some studies have found opposite or null associations for

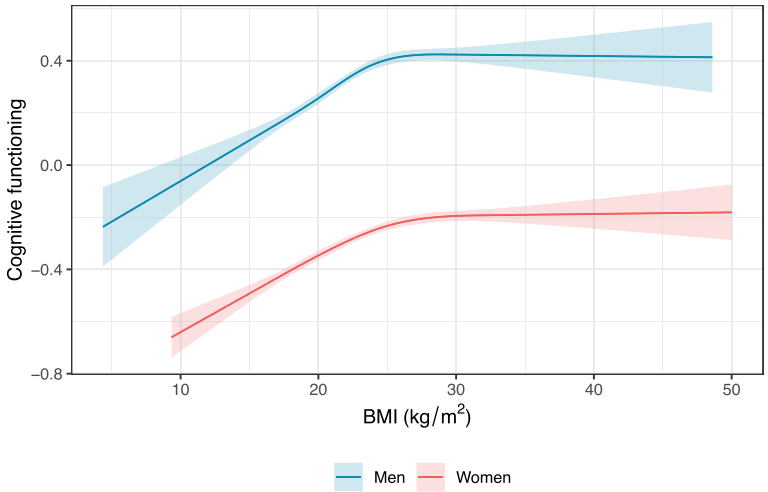

Fig. 2 Marginal predictions showing the nonlinear association between body-mass index (BMI) and cognition by gender from linear regression models with splines. Models were stratified by gender and adjusted for continuous age (spline), educational attainment, state, rural/urban residence, marital status, literacy, caste, paternal education, per capita consumption quintile, housing materials, smoking status, depressive symptoms, and moderate and vigorous physical activity

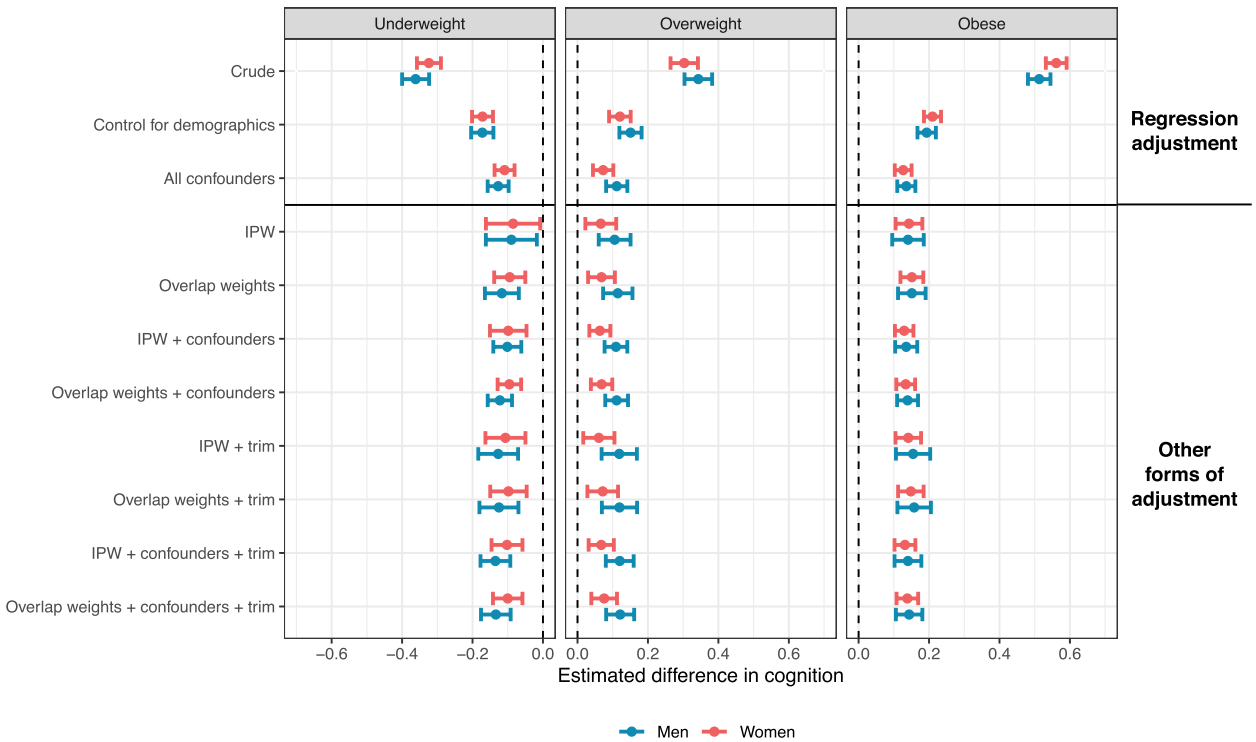

Fig. 3 Coefficient estimates for the association between body-mass index (BMI) category and cognition by gender from linear regression models. Results from the various analytic approaches are compared. Models that use weighting and additional adjust for confounders are noted by the presence of the term "+ confounders." Models adjusting for demographic variables adjusted for continuous age (spline), and educational attainment. The full adjustment set additionally included state, rural/urban residence, marital status, literacy, caste, paternal education, per capita consumption quintile, housing materials, smoking status, depressive symptoms, and moderate and vigorous physical activity. Models for weights also included interaction terms between age and both education and rural/urban residence. IPW = Inverse probability weighting

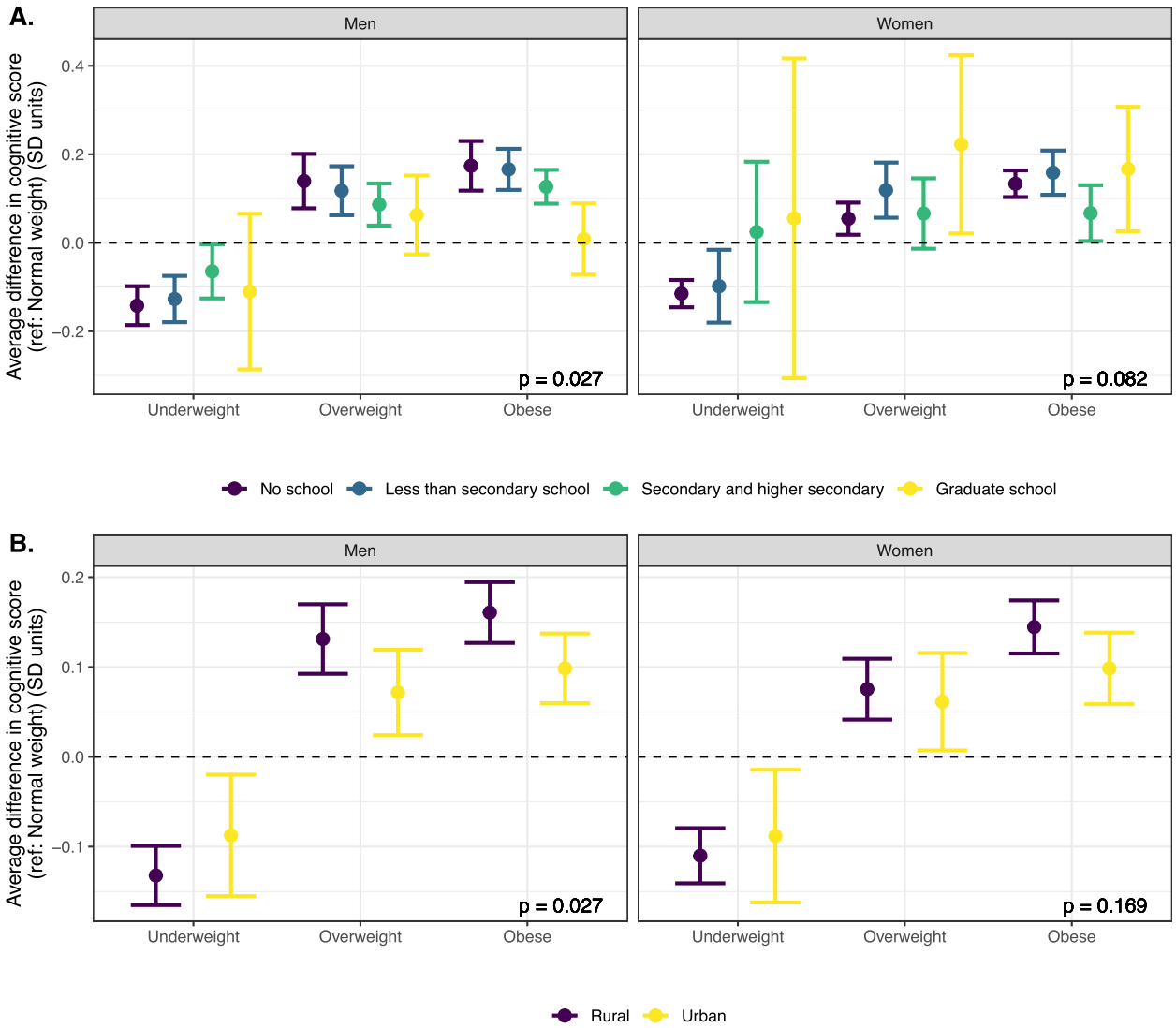

Fig. 4 Estimates of the association between body-mass index (BMI) and cognition by gender and by educational attainment (**A**) and rural/urban residence (**B**). P-values are derived from chi-squared tests and quantify the overall statistical significance of including the interaction term

overweight and obese BMI [15, 16], discrepant findings may be explained by differences in the operationalization of BMI as an exposure (categorical or continuous), the cognitive outcome used, or the age distributions of cohorts [31, 41].

Evidence that underweight BMI is strongly associated with lower cognition and worse cognitive outcomes has been more consistent [18, 42, 43]. Findings from the present study, coupled with the high prevalence of underweight BMI in low-income settings [44], highlight the importance of this high-risk group. Underweight BMI in these contexts likely serves as a marker for poor nutrition and life-course disadvantage. Individuals with underweight BMI should be targeted for interventions and programs seeking to support individuals at high risk for poor cognitive outcomes and dementia in later life. Additionally, future research should seek to understand the specific features of poor nutrition and life-course disadvantage (e.g. iron deficiency) that have the largest contributions to late-life cognitive health.

Results from analyses to better understand potential biases lend insights into potential explanations for observed positive associations between overweight and obese BMI and higher levels of cognitive functioning. Analyses using IPW, overlap weighting, or trimming yielded consistent results, and E-values indicated that unmeasured confounders would have to have a relative risk (or relative risk equivalent) of at least 1.40 with both the exposure and outcome to fully explain results. Although our set of measured confounders likely does

not capture all facets of SES, we included a large and diverse set of potential SES influences. Taken together, results indicate that while unmeasured confounding may partially explain the observed positive association, there are likely other factors as well. Observed positive associations between overweight and obese BMI and cognitive functioning were attenuated after excluding those with low cognition, indicating a potential role for reverse causation.

Associations between BMI and cognition were not present or significantly attenuated in those with higher educational attainment or in urban settings. Effect modification could be due to differences across groups in two potential sources of bias: 1) residual and unmeasured confounding and 2) reverse causation. Residual and unmeasured confounding may be different across groups if there is less variability in unmeasured SES factors within groups living in urban settings or with high educational attainment. Reverse causation may also be different across groups if groups have different levels of cognitive reserve. Reverse causation describes bias that arises because of capturing the effect of cognition on BMI when researchers are truly interested in the impact of BMI on cognition. Prior evidence indicates that reverse causation can have large impacts on observed associations between BMI and cognition because subtle changes in cognition early in the disease process may lead to weight loss [23, 24, 31]. However, cognitive reserve may modify this mechanism because those with high cognitive reserve may retain cognitive abilities longer before declining more rapidly [36]. Such modifications to the disease trajectory among those with high reserve (those with higher educational attainment, or those living in urban areas, which may be more cognitively stimulating), may explain both effect modification findings and the overall positive associations between overweight and obesity and cognitive functioning observed across studies [12, 20, 38–40].

Study limitations should be considered. Although future longitudinal data collection efforts are planned, currently the LASI study has collected only cross-sectional data. Therefore, we cannot establish appropriate temporality between our hypothesized exposure (BMI) and outcome (cognitive functioning) and concerns about reverse causation are amplified. However, in this study we probed reverse causation using multiple follow-up analyses, improving on prior cross-sectional studies in India and other low- and middle-income settings. Future studies should conduct longitudinal analyses when adequate follow-up time becomes available. Additionally, some measurement error in the assessment of cognitive functioning likely exists and may be differential by education and/or literacy. Despite the likely presence of some error, we minimized measurement error by using advanced methods for the quantification of cognition. We also showed estimated cognitive scores were not sensitive to the inclusion of items requiring literacy.

Conclusions

In summary, we found associations between underweight BMI and lower cognitive functioning as well as overweight and obese BMI and higher cognitive functioning in India. Individuals with underweight BMI are at higher risk for poor cognitive outcomes and should be the target of interventions and support programs. Based on a wide array of supplementary and probing analyses and contextual evidence from other studies, we believe findings of positive associations between overweight and obese BMI and cognitive functioning may be due to a combination of unmeasured confounding and reverse causation. Future studies in low- and middle-income countries with extended longitudinal follow-up would help further tease apart sources of bias and establish causal relationships in these settings.

Abbreviations

BMI	Body Mass Index
SES	Socio-Economic Status
LASI	Longitudinal Aging Study in India
CIDI-SF	Composite Diagnostic Interview – Short Form

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20101-y.

Supplementary Material 1.

Acknowledgements

We thank Dr. Marco Angrisani for constructing sample weights and all LASI and LASI-DAD team members and collaborators for their contribution to the wave 1 LASI and LASI-DAD data collection.

Authors' contributions

E.N. conceptualized and designed the study, conducted the analysis, and wrote and edited the manuscript. A.L.G. conducted analysis and reviewed the manuscript. P.H. supervised the study, provided critical feedback on study methods and analysis, and reviewed the manuscript. J.L. acquired study funding, supervised the study, provided critical feedback on study methods and analysis, and reviewed the manuscript. T.V.S. and A.B.D. acquired study funding, supervised the study, and reviewed the manuscript.

Funding

LASI data collection was funded by the National Institute on Aging, National Institutes of Health (NIA/NIH), U.S.A. (R01AG042778); the Ministry of Health and Family Welfare, Government of India (T22011/02/2015-NCD). The NIA/NIH provided funding for a nationally representative sample, drawing samples from the 15 largest states. The Government of India provided additional funding to make the study representative of each state and union territory and enable oversampling of older adults and four metropolitan cities. LASI data processing was funded by the National Institute on Aging, National Institutes of Health (NIA/NIH) (R01AG030153). LASI-DAD data collection was funded by the National Institute on Aging, National Institutes of Health (NIA/NIH), U.S.A. (R01AG051125, U01AG065958). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Availability of data and materials
LASI data used in this study are publicly available on the websites of the Gateway to Global Aging Data (https://g2aging.org/) and International Institute for Population Sciences (IIPS; https://www.iipsindia.ac.in/content/LASI-data). To access data, users must register, provide an email address, and sign a data use agreement.

Declarations

Ethics approval and consent to participate
LASI obtained approval from the University of Southern California Institutional Review Board (IRB) (UP-CG-14_00005), the Harvard University IRB (CR- 16715-10), the International Institute for Population Sciences IRB (Sr. No. 12/1054), and Health Ministry's Screening Committee clearance from the Indian Council of Medical Research (F.No.T.21012/07/ 2012-NCD). All participants gave informed consent to participate (written or thumb print).

Competing interests
The authors declare no competing interests.

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Received: 7 July 2023 Accepted: 16 September 2024
Published online: 05 October 2024

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