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THE EFFECT OF VARIATION IN BODY MASS INDEX ON LOWER URINARY TRACT SYMPTOMS IN WOMEN: CAUSAL ESTIMATES FROM A MENDLELIAN RANDOMIZATION APPROACH

Hypothesis / aims of study

Despite consistent associations from cross-sectional studies between body mass index (BMI) and "all cause" urinary incontinence (UI) in women, longitudinal observational studies have reported inconsistent effects of variation in BMI on individual subtypes of UI[1,2]. Associations between BMI and other storage or voiding lower urinary tract symptoms (LUTS) in women have received limited attention. Overall evidence of a causal association between BMI and LUTS from observational studies may be limited by unmeasured confounding, reverse causality, and differential loss to follow up. Mendelian Randomization has been suggested as one approach to improve causal inference from observational studies.

Mendelian Randomization uses genetic variants that are robustly associated with the exposure of interest (here BMI) as proxies (instrumental variables) to determine the causal effect of this exposure on an outcome (here individual LUTS). Due to random assortment of alleles during gamete formation, genetic risk variants are independent of confounding environmental risk factors. Furthermore genetic risk variants are not influenced by reverse causation from their associated phenotypes. In this analysis we use 32 genetic variants with replicated associations with increased BMI[3] as instrumental variables to test whether there is a linear causal effect of BMI on self-reported LUTS in large population based cohort of women.

Study design, materials and methods

The Avon Longitudinal Study of Parents and Children (ALSPAC) initially recruited pregnant women expected to deliver between April 1991 and December 1992. LUTS were self-reported at median 12 year follow up, using a postal questionnaire including 14 items from the validated Bristol Female Lower Urinary Tract Symptom (BFLUTS) questionnaire. Most items from that questionnaire follow the response categorisation of the stress incontinence item "Does urine leak when you are physically active, exert yourself, cough or sneeze?" (responses: "never", "occasionally", "sometimes", "most of the time", "all of the time"). For these items we classified women reporting symptoms ≥sometimes as cases. For nocturia we classified women reporting ≥2 voids/night as cases. For daytime frequency we classified women reporting ≥9 voids/day as cases. BMI was calculated using self-reported height and weight at median 12 years following delivery. Genotyping was conducted using Illumina 610 BeadChips with imputation using MACH. A genetic susceptibility score for increased BMI was calculated using a panel of 32 Single Nucleotide Polymorphisms (SNPs) associated with increased BMI in a previous large meta-analysis[3]. The genetic susceptibility score for each individual was derived from the number of BMI risk alleles weighted by the effect of each allele on BMI from previously published data.

We conducted a complete case analysis for 4,898 women with available genotypes, BMI, self-report of LUTS, and covariates. We used multivariable logistic regression to test associations between BMI and each LUTS, adjusting for age, educational level, parity, and mode of delivery. To test that the assumptions of the Mendelian Randomization model were met, we tested for associations between genetic susceptibility score and important risks for LUTS including age and parity. We used the logistic control function estimator to derive the instrumental variable estimate of the effect of BMI on each LUTS. Finally we used the Hausman test to assess equality of the logistic regression and instrumental variable estimates. All analyses were performed using Stata 12.

Results

Participants reported LUTS at median age 40 (range 27-56). There were statistically significant positive associations between the BMI genetic susceptibility score and only two symptoms: nocturnal enuresis and unconscious incontinence, equivalent to 6% increased risk per allele. In conventional multivariable analyses BMI was positively associated with all subtypes of UI, and all storage symptoms except daytime frequency (see table). The largest observational effects were again for nocturnal enuresis and unconscious UI, equivalent to 11-13% increased risk per unit increase in BMI. The Mendelian Randomization causal estimates were all consistent with either no association or the observational associations, with the exception of urgency UI, where the causal estimate suggests a negative association with BMI (Hausman p=0.02).

	Observational Estimate		Causal Estimate		
	Multivariable logistic regression		Logistic control function estimator		Hausman test
Phenotype	aOR	95%CI	OR	95%CI	p
Stress UI	1.045*	1.031-1.060	1.002	0.915-1.097	0.52
Urgency UI	1.057*	1.043-1.071	0.940	0.854-1.034	0.02
Frequency	1.015	0.997-1.033	0.998	0.880-1.13	0.80
Nocturia >=2	1.104*	1.080-1.129	1.010	0.837-1.219	0.37
Urinary Urgency	1.039*	1.019-1.059	1.041	0.892-1.216	0.98

Unconscious UI	1.132*	1.095-1.170	1.400	0.966-2.030	0.23
Hesitancy	0.996	0.962-1.031	0.946	0.743-1.205	0.62
Straining	1.013	0.956-1.074	0.815	0.500-1.329	0.32
Nocturnal Enuresis	1.111*	1.075-1.148	1.387	0.969-1.986	0.20
Burning	1.019	0.997-1.041	0.929	0.787-1.097	0.26
Incomplete Emptying	1.044*	1.022-1.065	1.126	0.953-1.332	0.36
Intermittency	0.977	0.933-1.022	1.132	0.830-1.546	0.41

Table: Observational and causal estimates of associations between BMI and LUTS. Hausman test compares models. (*p<0.001)

Interpretation of results

These results confirm observational estimates of positive associations between BMI and major LUTS from previous studies, and extend significant findings even to rare symptoms such as nocturnal enuresis and unconscious UI. Even with use of all replicated increased BMI susceptibility SNPs, the genetic susceptibility score accounts for only 1.5% of phenotypic variation in BMI. Thus despite the large sample to test observational associations, the Mendelian Randomisation estimates remain significantly underpowered. For most symptoms we found no evidence that causal estimates differed statistically from the observational estimates, but for urgency UI these results suggest no causal effect from BMI.

Concluding message

In a large population based cohort of women, consistent estimates were obtained for direct associations of most individual LUTS with BMI, and associations mediated through genetic BMI risk variants. However, observational associations between BMI and urgency UI, as found in this sample, may result from unmeasured confounding or reverse causality.

References

1. Obesity 2008;16(4):881-6
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