Causal effects of body mass index on airflow obstruction and forced mid-expiratory flow: a Mendelian randomization study taking interactions and age-specific instruments into consideration toward a life course perspective

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Author(s) Probst-Hensch, N.; Jeong, A.; Stolz, D.; Pons, M.; Soccal, P. M.; Bettschart, R.; Jarvis, D.; Holloway, J. W.; Kronenberg, F.; Imboden, M.; Schindler, C.; Lovison, G. F.

Author(s) at UniBasel Probst-Hensch, Nicole ; Jeong, Ayoung ; Imboden, Medea ; Schindler, Christian ; Lovison, Gianfranco ;

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Mesh terms Adult; Age Factors; Body Mass Index; Cross-Sectional Studies; Female; Humans; Lung; Mendelian Randomization Analysis; Pulmonary Disease, Chronic Obstructive

Obesity has complex links to respiratory health. Mendelian randomization (MR) enables assessment of causality of body mass index (BMI) effects on airflow obstruction and mid-expiratory flow. In the adult SAPALDIA cohort, recruiting 9,651 population-representative samples aged 18-60 years at baseline (female 51%), BMI and the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) as well as forced mid-expiratory flow (FEF25-75%) were measured three times over 20 follow-up years. The causal effects of BMI in childhood and adulthood on FEV1/FVC and FEF25-75% were assessed in predictive (BMI averaged over 1st and 2nd, lung function (LF) averaged over 2nd and 3rd follow-up; N = 2,850) and long-term cross-sectional models (BMI and LF averaged over all follow-ups; N = 2,728) by Mendelian Randomization analyses with the use of weighted BMI allele score as an instrument variable and two-stage least squares (2SLS) method. Three different BMI allele scores were applied to specifically capture the part of BMI in adulthood that likely reflects tracking of genetically determined BMI in childhood. The main causal effects were derived from models containing BMI (instrumented by BMI genetic score), age, sex, height, and packyears smoked as covariates. BMI interactions were instrumented by the product of the instrument (BMI genetic score) and the relevant concomitant variable. Causal effects of BMI on FEV1/FVC and FEF25-75% were observed in both the predictive and long-term cross-sectional models. The causal BMI- LF effects were negative and attenuated with increasing age, and stronger if instrumented by gene scores associated with childhood BMI. This non-standard MR approach interrogating causal effects of multiplicative interaction suggests that the genetically rooted part of BMI patterns in childhood may be of particular relevance for the level of

small airway function and airflow obstruction later in life. The methodological relevance of the results is first to point to the importance of a life course perspective in studies on the etiological role of BMI in respiratory health, and second to point out novel methodological aspects to be considered in future MR studies on the causal effects of obesity related phenotypes.
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