# Letter to the Editor

## Assessment of a causal relationship between body mass index and atopic dermatitis

*To the Editor:*

Atopic dermatitis (AD) is an itchy, inflammatory skin condition associated with multiple comorbidities. Observational epidemiology suggests an increased prevalence of obesity in patients with AD, but (1) whether there is a causal effect and (2) whether obesity leads to AD or *vice versa* remain unclear. Genetic predisposition to obesity has been shown to promote psoriasis,[1] but dermatologic disorders can also lead to reduced participation in physical activity, resulting in weight gain. We aimed to investigate evidence of causality in the association of AD with elevated body mass index (BMI).

We meta-analyzed 33 published studies examining the association between obesity or elevated BMI and AD to summarize available observational data (see Fig E1 in this article's Online Repository at www.jacionline.org). The odds ratio (OR) for AD in overweight individuals was 1.05 (95% CI = 0.94-1.19) in adults (n = 51,008) and 1.08 (95% CI = 1.00-1.16) in children (n = 506,202) (see Fig E2 in this article's Online Repository at www.jacionline.org). For obese individuals, the OR for having AD was 1.19 (95% CI = 0.95-1.49) in adults (n = 1,400,679) and 1.20 (95% = CI 1.11-1.30) in children (n = 796,514) (see Fig E3 in this article's Online Repository at www.jacionline.org); the methods and results are detailed in the Methods and Results sections of the Online Repository (at www.jacionline.org). We extended the observational analysis by using 2 large population-based studies from the United Kingdom and Norway[2,3] (for details, see the Online Repository and Tables E1-E4). Among overweight individuals (BMI of 25-30 kg/m$^2$), the OR of AD was 1.02 per each 1-kg/m$^2$ increase in BMI (95% CI = 1.00-1.04; $P$ = .07; 4,820 cases and 130,776 controls); a similar estimate was found among obese individuals (BMI >30 kg/m$^2$) (ie, OR =1.02 [95% CI = 1.01-1.03; $P = 3.3 \times 10^{-4}$] in a sample of 2,741 cases and 73,907 controls) (see Fig E4 in this article's Online Repository at www.jacionline.org).

Observational epidemiology has several limitations, including bias from confounding and reverse causation; this restricts its utility for causal inference. However, causality and the direction of effect can be investigated by mendelian randomization (MR). MR uses genetic variants as a proxy for the exposure (eg, BMI) to estimate the effect on an outcome (eg, AD). Genetic variants are randomly allocated at fertilization, therefore avoiding confounding; they are not affected by outcomes later in life, thus avoiding reverse causation. Genome-wide association studies (GWASs) have identified single-nucleotide polymorphisms (SNPs) associated with BMI (≤941 loci[4,5]) and AD (24 loci in European populations[6]). These SNPs can be combined into a genetic risk score (GRS) or "genetic instrument" that acts as a proxy for the specified trait during MR.

We conducted MR analysis by using data from the largest population-based studies in the United Kingdom (UK Biobank[2]) and Norway (Nord-Trøndelag Health Study, Norway[3] [HUNT, 2006-08]) along with the largest published GWASs for BMI[4,5] and AD[6] to date, representing a total of 742,611 individuals (see Table E5 in this article's Online Repository at www.jacionline.org). One-sample MR was performed in the UK Biobank and HUNT data sets with the individuals' BMI SNPs, measured BMI, and AD status. Two-sample MR using published GWAS data[4-6] was performed and meta-analyzed with the 1-sample estimate to obtain an overall causal estimate. Similarly, reverse MR was conducted to investigate the effect of AD genetic risk on BMI. Methodologic details and sensitivity analysis are described in the Online Repository, including Fig E5.

The BMI GRS was strongly associated with BMI in both the UK Biobank and HUNT data sets (see Figs E6 and E7 in this article's Online Repository at www.jacionline.org), supporting its use as a genetic instrument. Potential confounders of the GRS-BMI association were detected (see Figs E6-E9), but the magnitudes were minimal in comparison with the strength of association with BMI. Similarly, the AD GRS was a good predictor of AD in both the UK Biobank (OR = 1.26 [95% CI = 1.23-1.28]; F-statistic = 2036; $R^2$ = 0.7%) and HUNT (OR = 1.15 [95% CI = 1.11-1.21]; F-statistic = 97; $R^2$ = 0.4%) data sets, despite lacking an *FLG* null genotype (R501X/rs61816761), which is known to show strong association with AD.

Meta-analyzed 1- and 2-sample MRs show evidence of a small causal effect of higher BMI increasing the risk of AD (OR = 1.02 [95% CI = 1.00-1.04]; $P$ = .03) (Fig 1). This represents an increase in AD risk by approximately 2% for each 1-kg/m$^2$ increase in BMI, which is remarkably similar to the observational estimate (see Figs E2 and E3 in the Online Repository). Importantly, sensitivity analyses showed little evidence of pleiotropy (for details, see the Sensitivity Analysis section, Table E6, Fig E10, and Fig E11 in this article's Online Repository at www.jacionline.org) or heterogeneity among the individual SNP effect estimates (UK Biobank Q = 101.07 [$P$ = .32]; HUNT Q = 100.04 [$P$ = .37]). Two-sample MR using the larger number of recently published BMI SNP estimates (941 SNPs)[4] gave similar evidence of a causal effect on AD risk (OR = 1.08 [95% CI = 1.01-1.16]; $P$ =.02).

In the reverse direction, meta-analysis gave weak evidence of a very small causal effect (Fig 2): a 0.03-kg/m$^2$ change in BMI per doubling odds of AD (95% CI = –0.02 to 0.08; $P$ = .24). There was little evidence of pleiotropy but modest heterogeneity among the individual SNP effects (see Fig E12 and Table E7 in in this article's Online Repository at www.jacionline.org). The difference in BMI between patients with AD and controls estimated in 1-sample MR (0.15 kg/m2, 95% CI -1.97 to 2.27) was small compared with observational estimates (see Tables E1 and E2), indicating that the association is mainly explained by the causal effect of BMI on AD.

The association of obesity with cardiometabolic disease and systemic inflammation is now well recognized, and clinical guidelines recommend screening patients with psoriasis for obesity. The presence of a *causal* effect and the *direction* of effect are both clinically relevant, to define a primary target (ie, obesity) for intervention. Our MR analysis shows evidence that higher

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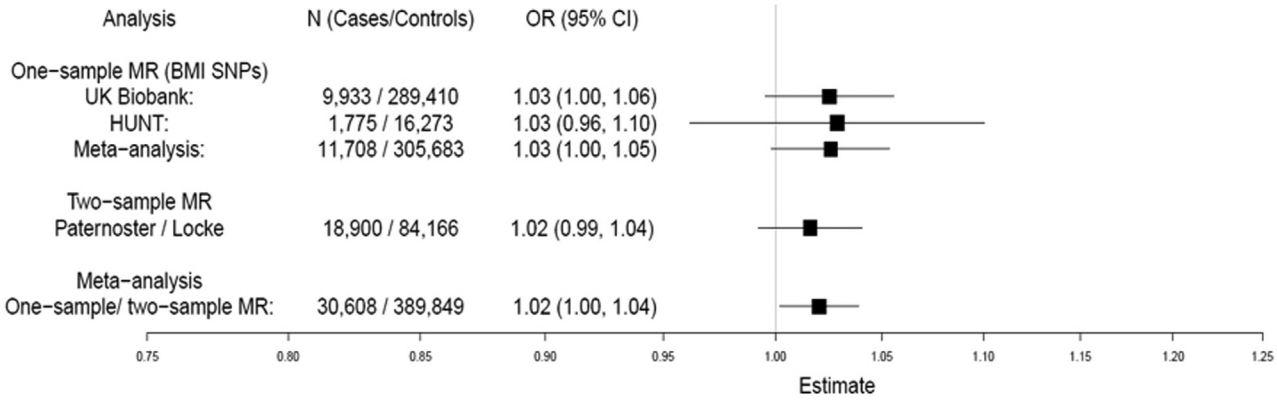


**FIG 1.** MR analysis of the causal effect of BMI on AD. Meta-analysis of 1-sample and 2-sample MR estimates using individual BMI SNPs as instruments. Estimates are given per 1-kg/m$^2$ increase in BMI.

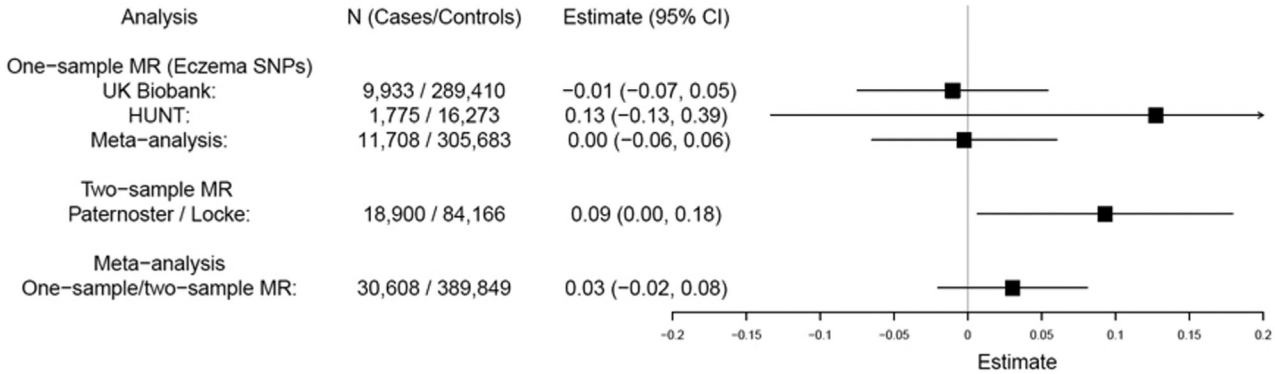


**FIG 2.** Reverse direction MR analysis: effect of AD genetic risk on BMI. Meta-analysis of 1-sample and 2-sample MR estimates using individual AD SNPs as instrumental variables. Estimates represent change in BMI (kg/m$^2$) per doubling odds of AD.

BMI increases the risk of AD (ie, a 2% increase in disease risk for each 1-kg/m$^2$ increase in BMI). Conversely, there was no strong evidence of a causal effect of AD genetic risk on BMI; the estimate of 0.03 kg/m$^2$ suggests that genetic risk for AD has little meaningful influence on an individual's BMI. These findings may be compared with the causal effect of BMI on psoriasis and lack of effect of psoriasis genetic risk on BMI.[1] The effect of BMI on AD is more modest than the effect size observed in psoriasis, but the high prevalence of obesity (in more than one-third of US adults) and AD (in ≤10% of adults) demonstrate the potential importance of this causal effect on a population scale.

The molecular mechanisms by which obesity contributes to skin inflammation remain unclear. Excess adipose tissue secretes proinflammatory cytokines and hormones,[7] and atopic inflammation may be promoted by disruption of the epidermal barrier in obese individuals.[8] Changes in the adipocytes and lymphatic vessels may also contribute to obesity-related skin inflammation.[8] Research to define mechanisms underlying the causal relationship demonstrated by MR may identify novel therapeutic targets.

Our MR analyses have various strengths as well as weaknesses. The large sample size is powerful, and the genetic instruments are strong. The 2-sample analysis included an overlap of data sources (from the HUNT study), which has the potential to bias the causal estimate, but this bias would be in the direction of the null. There is the possibility of misclassification of AD, and because AD often shows remission in childhood, this phenotype may be particularly susceptible to recall bias in adult studies; however, this would likely drive any estimate toward the null. It is also important to note that the MR methodology applied here does not define temporal relationship. Genetic risk has a lifetime effect and therefore predates disease onset, but a causal effect determined by MR does not rely on obesity occurring before the onset of AD. However, when we attempted to mitigate this issue by repeating the MR analyses using SNPs that are strongly associated with childhood BMI,[9] a causal estimate with the same direction of effect was obtained (OR = 1.04; 95% CI = 1.01-1.07; $P$ = .01). Nevertheless, replication of these analyses within pediatric cohorts with large sample sizes would be valuable future work.

In conclusion, we have found evidence of a small but potentially important causal effect of BMI on AD. Clinical trials have shown that interventions to promote weight loss can lead to improvement in psoriasis, but this approach has not been tested in AD. The results of our study provide support for the investigation of obesity management strategies and/or targeting of the adipocyte-keratinocyte cross-talk as therapeutic opportunities for AD. This may contribute to the prevention of AD, as well as to a reduction in the population prevalence of this chronic disease.

This research was conducted by using data from the UK Biobank Resource (application number 10074) and the Nord-Trøndelag Health Study (the HUNT Study). Details of patient and public involvement in the UK Biobank are available online (http://www.ukbiobank.ac.uk/about-biobank-uk/ and https://www.ukbiobank.ac.uk/wp-content/uploads/2011/07/Summary-EGF-consultation.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6). The UK Biobank data set used to conduct the research in this article is available via application directly to the UK Biobank. Applications are assessed for meeting the required criteria for access, including legal and ethics standards. More information regarding data access can be found at the following website: http://www.ukbiobank.ac.uk/scientists-3/. Data from the HUNT Study used in research projects will, when reasonably requested by others, be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (available at: http://www.ntnu.edu/hunt/data) describes in detail the policy regarding data availability. No patients were specifically involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of this study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants, but the UK Biobank and the HUNT Study disseminate key findings from projects on their websites. The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. We acknowledge the permission of the EAGLE consortium (including 23andMe) to use results from their previous GWAS of AD (Paternoster et al[6]).

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## Assessment of a causal relationship between body mass index and atopic dermatitis

Budu-Aggrey *et al.*

## Supplementary Methods and Results

### *Literature review*

We searched for published studies that compared BMI, overweight or obesity rates between individuals with AD and controls. All studies identified in a PubMed search were considered for review. PubMed was searched on 18/11/2016 with the terms "(eczema OR atopic dermatitis AND (obesity OR overweight OR BMI)". We included studies with any operationalized definition of AD, since 'atopy' is often not clearly defined. We also included studies with cases meeting this definition of AD plus a control group without AD; that presented data for a BMI-related trait within the AD and control groups. Studies were excluded if they did not present data for both groups; if they matched individuals with AD and controls on BMI; or if cases and controls were both drawn from a disease sub-population. We did not exclude studies where participants may have had incidental comorbidities. We extracted the location of the study, the study name (if applicable), age of the study population, features of the control group (for example, if they were drawn from another dermatological population), the type of study, how AD was defined (if it was current, recent, or lifetime disease), the covariates used in the analysis, and the definition of overweight and/or obesity used by the study.

The definitions used for obesity and being overweight were based on international guidelines[1] or study-specific thresholds. Where stated, for the majority of studies BMI greater than 25 kg/m$^2$ was used to define being overweight, while BMI greater than 30 kg/m$^2$ was used to define obesity.

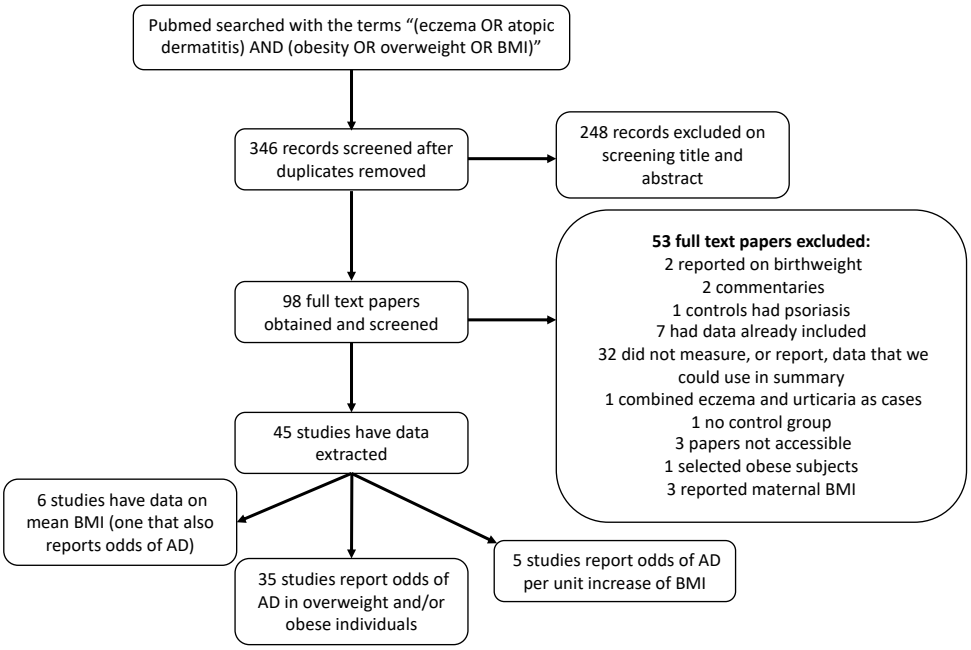


**Figure E1. Flow diagram summarising literature review**

### *Studies reporting the odds of AD in overweight and obese adults*


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### *Studies of AD in overweight and obese paediatric cases*


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Sybilski AJ, Raciborski F, Lipiec A, et al. Obesity – a risk factor for asthma, but not for atopic dermatitis, allergic rhinitis and sensitization. Public Health Nutr 2015;18:530–6. doi:10.1017/S1368980014000676

Lei Y, Yang H, Zhen L. Obesity is a risk factor for allergic rhinitis in children of Wuhan (China). Asia Pac Allergy 2016;6:101. doi:10.5415/apallergy.2016.6.2.101


Six studies reported the mean difference in BMI between AD cases and controls (**Table E1**). These studies showed mixed results, but the majority (4 out of 6) reported mean BMI to be lower in AD cases compared to controls. Kusunoki *et al.* reported the odds of AD in children to be 1.02 per 1 kg/m$^2$ increase in BMI,[2] and the same direction of effect was observed in overweight and obese children (Fig 2). The remaining 5 studies reported the odds of AD with higher BMI (**Table E2**), where the majority (4 out of 5) estimates gave evidence of increased AD risk.

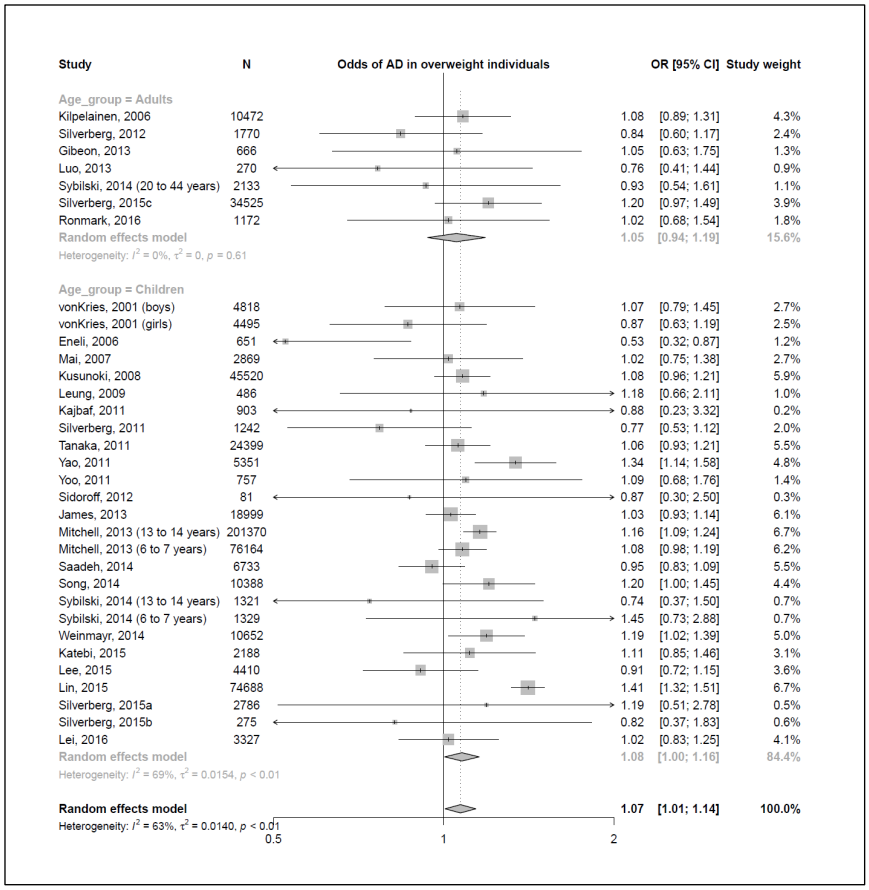


**Figure E2. Observational association between being overweight and having AD: meta-analysis of the odds of AD in overweight individuals.** CI, confidence interval; OR, odds ratios; top forest plot shows studies of adults, lower plot shows studies of children, final estimate is meta-analysis of both sets of data.

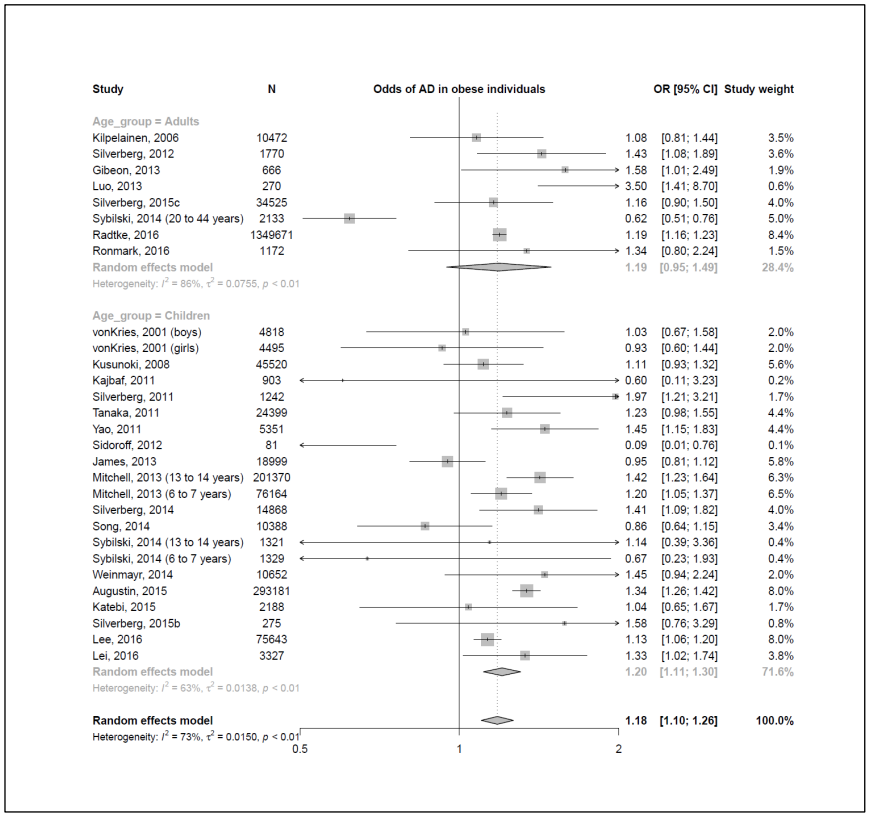


**Figure E3. Observational association between obesity and AD: meta-analysis of the odds of AD in obese individuals.** CI, confidence interval; OR, odds ratio; top forest plot shows studies of adults, lower plot shows studies of children, final estimate is meta-analysis of both sets of data.

| Study | Age group | Mean difference (95% CI) |
|---|---|---|
| Ellison (Males), 2006 | Children | 0.44* |
| Ellison (Females), 2006 | Children | -0.18* |
| Kusunoki, 2008 | Children | -0.10 (-2.47, 2.27) |
| Machura, 2013 | Children | -0.66 (-4.89, 3.57) |
| Kim, 2015 | Adults | -0.06 (-3.89, 3.77) |
| Lee (Males), 2016 | Adults | -0.20 (-6.66, 6.26) |
| Lee (Females), 2016 | Adults | 0.60 (-4.67, 5.87) |
| D'Auria, 2017 | Children | -0.05*+ |

**Table E1. Reviewed studies reporting the difference in BMI (kg/m$^2$) between AD cases and controls.** CI, confidence interval; *Unable to estimate 95% confidence interval; +Mean difference in BMI z-score.

| Study | Age group | OR (95% CI) |
|---|---|---|
| Lee, 2001 | Children | 1.29 (1.15, 1.44) |
| Irei, 2005 | Children | 1.02 (0.70, 1.47) |
| Purvis, 2005 | Children (BMI >18 kg/m$^2$) | 0.28 (0.07, 1.16) |
| Murray, 2010 | Children | 1.79* (1.03, 3.13) |
| Byberg, 2016 | Children | 1.32** (1.06, 1.65) |

**Table E2. Reviewed studies reporting the odds of AD per unit increase in BMI (kg/m$^2$)** CI, confidence interval; *per unit increase in BMI z-score; **per unit increase in BMI standard deviation score

**References**


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Lee S Il *et al.*. J Korean Med Sci. 2001;16:155.
Irei A V *et al.* Eur J Clin Nutr. 2005;59:571–7.
Purvis DJ *et al.* Br J Dermatol. 2005;152:742–9.
Murray CS *et al.* Clin Exp Allergy. 2011;41:78–85.
Byberg KK *et al.* Clin Transl Allergy. 2016;6:33.


***Meta-analysis of published studies***

All data pertaining to BMI and AD were extracted and a meta-analysis was performed for the definition with the most available data, this being the odds of AD in overweight and/or obese individuals. This analysis represents an update of the 2015 review by Zhang *et al*.[3] The meta-analysis was conducted separately for children and adults, as well as combined. A random effects model was used due to the inclusion of heterogeneous populations and study designs being meta-analysed.

The overall OR for AD in overweight individuals was 1.05 (95% CI 0.94 to 1.19) in adults (n=51,008) and 1.08 (95% CI 1.00 to 1.16) in children (n=506,202) (**Figure E2**). For obese individuals, the OR for having AD was 1.19 (95% CI 0.95 to 1.49) in adults (n=1,400,679) and 1.20 (95% CI 1.11 to 1.30) in children (n=796,514) (**Figure E3**). Where stated, children were defined as those under 18 years of age, although one paediatric study included individuals aged up to 19 years.[4] Adults were defined as those aged 18 years and above in studies where this had been described.

***Observational analysis using UK Biobank and HUNT datatsets***

*Clinical outcomes*

The BMI of UK Biobank participants was calculated from standing height and weight measurements that were taken while visiting an assessment centre. Individuals were defined as having atopic dermatitis (AD) based on their response during a verbal interview with a trained member of staff at the assessment centre. Participants were asked to tell the interviewer which serious illnesses or disabilities they had been diagnosed with by a doctor and were defined as AD cases if this disease was mentioned. Disease information was also obtained from the Hospital Episode Statistics (HES) data extract service where health-related outcomes had been defined by International Classification of Diseases (ICD)-10 codes (**Table E3**). Additionally, if any had answered "yes" to "Has a doctor ever told you that you have hay fever, allergic rhinitis or eczema", then these individuals were excluded from the AD controls.

| Phenotype | ICD10 codes |
|---|---|
| Atopic dermatitis | L20 |
| Besnier's prurigo | L20-L200 |
| Other atopic dermatitis | L20-L208 |
| Atopic dermatitis, unspecified | L20-L209 |

**Table E3. International Classification of Diseases (ICD)-10 codes used to obtain disease information for AD (eczema; atopic eczema; atopic dermatitis) from the UK Biobank resource**

Within HUNT, participants' height and weight were measured and used to calculate BMI (kg/m$^2$). Participants were defined as AD cases based on their response to a general questionnaire sent to all HUNT participants. AD cases responded affirmatively to both "Have you had or do you have any of the following diseases: Eczema on hands" and "Did you have eczema when you were a child? (also called atopic eczema)". In addition, cases were obtained from the Nord-Trøndelag Health Trust which includes the two hospitals (Levanger and Namsos) in the study area, and the General Practitioner records. Disease classifications are shown in **Table E4**.

| Phenotype | ICD10 | ICD9 | ICPC-2 |
|---|---|---|---|
| Atopic dermatitis | L20 | | |
| Other and unspecified dermatitis | L30 | | |
| Atopic dermatitis and related conditions | | 691 | |
| Atopic dermatitis/eczema | | | S87 |

**Table E4. International Classification of Diseases (ICD) and International Classification of Primary Care-2 (ICPC-2) codes used to obtain disease information for AD (eczema; atopic eczema; atopic dermatitis) from the HUNT study**

*Confounder variables*

Within UK Biobank, confounders that were considered in the current study were age, sex, smoking status, alcohol intake and educational attainment. The age and sex of participants were baseline characteristics determined at recruitment. The information on age was coded and analysed as a continuous variable, while sex was analysed as a binary variable. Smoking status, alcohol intake and educational attainment were defined by responses to a touchscreen questionnaire. The smoking status of participants was summarised as being a current or previous smoker, or never smoked, where this information was coded into a categorical variable. Alcohol intake frequency was determined by asking participants "about how often do you drink alcohol?", where options included "Daily or almost daily", "Three or four times a week", "One to three times a month", "Special occasions only" and "Never". This information was categorised for daily, weekly and monthly alcohol intake. Educational attainment was also defined by asking "which of the following qualifications do you have?", where participants could select more than one option including "College or University degree", "A levels/AS levels or equivalent", "O levels/GCSEs or equivalent", "CESs or equivalent", "NVQ or HND or HNC or equivalent", "Other professional qualifications eg: nursing, teaching", or "None of the above". Participant responses were coded into categorical variables for degree holders, those who had completed advanced level studies (A-level) or had obtained their general certificate of secondary education (GCSE). Within HUNT, confounders considered in the current study were age, sex, smoking status and alcohol intake. Information on educational attainment was not available in the third survey of the HUNT study. The age and sex of participants were determined at the time of participation. The information on age was coded and analysed as a continuous variable, while sex was analysed as a binary variable. Smoking status and alcohol intake were defined by the participants' response to a questionnaire. Smoking status was defined as being never, former, occasional, or current smoker. Alcohol intake frequency was determined by asking participants "about how often in the last 12 months did you drink alcohol?", where options included "4-7 times a week", "2-3 times a week", "about once a month", "a few times a year", "not at all last year" and "never drunk alcohol".

*Meta-analysis*

Within the UK Biobank and HUNT datasets, logistic regression models were used to estimate the observational association between BMI and AD. This analysis was performed for all individuals, as well as for overweight (25 kg/m2<BMI<30 kg/m2) and obese (BMI>30kg/m2) individuals alone. Analyses were adjusted for age, sex, smoking status, alcohol intake and educational attainment (where information on education was available in UK Biobank only). The estimates for each dataset were meta-analysed assuming a random effects model to account for heterogeneity.

*Results*

There was very little evidence of an association between BMI and AD in UK Biobank, but some evidence within the HUNT dataset (**Figure E4**). Upon meta-analysis, the OR of AD per 1 kg/m$^2$ higher BMI was 1.01 (95% CI 1.00 to 1.01; *P*=0.26). Among overweight individuals (BMI = 25 to 30 kg/m$^2$), the OR of AD per 1 kg/m$^2$ higher BMI was 1.02 (95% CI 1.00 to 1.04; *P*=0.07; 4,820 cases; 130,776 controls). A similar estimate was found among obese individuals (BMI greater than 30 kg/m$^2$) but with stronger evidence of an association (OR=1.02; 95% CI 1.01 to 1.03; *P*=3.3x10$^{-4}$; 2,741 cases and 73,907 controls).

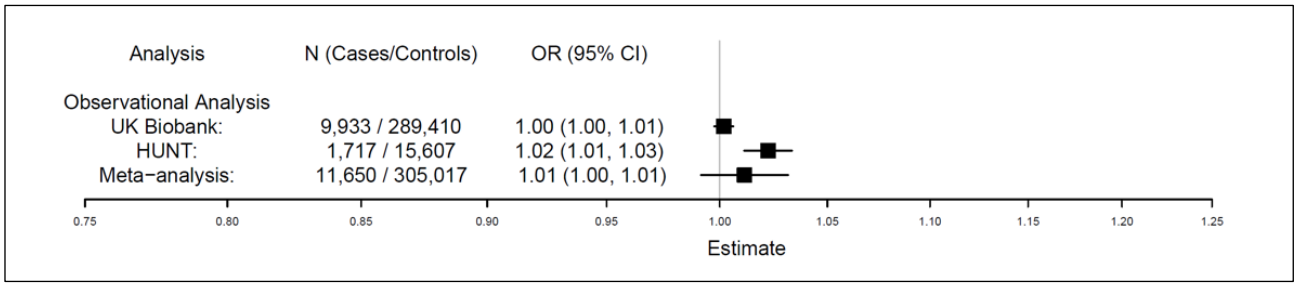


**Figure E4. Observational association between BMI upon AD in two population-based studies.** Association analysis and meta-analysis of observational data from the UK Biobank and HUNT study, Norway. Observational analysis was restricted to individuals with complete information on potential confounders. Estimates are given per 1kg/m$^2$ increase in BMI. CI, confidence interval.

***Analysis of causal relationships***

*Study populations and phenotypes*

Data were available, with written informed consent, for a total of 317,391 participants including 9,933 AD cases from the UK Biobank[5] aged 40-69 years and 1,775 AD cases from the third survey of the Nord-Trøndelag Health Study, Norway[6] (HUNT, 2006-08) aged 20 years and over (**Table E5**). AD in the UK Biobank was defined by patient-report of doctor diagnosis or hospital statistics using ICD-10 codes; in the HUNT study AD was defined by self-report and/or hospital statistics using ICD-9 and ICD-10 codes and/or diagnosed by general practitioners using ICPC-2 codes. Healthy controls were individuals from the same population-based studies, but without reported AD. All individuals included in this analysis were of white European ethnicity. The BMI (kg/m$^2$) of UK Biobank and HUNT participants was calculated from height and weight measurements. UK Biobank is approved by the National Health Service National Research Ethics Service (ref 11/NW/0382; UK Biobank application number 10074); the HUNT Study was approved by the Regional Committee for Medical and Health Research Ethics (REC Central), which also gave specific approval for this study (2015/2003). Summary level data were available for 425,220 individuals of European ancestry from published GWAS studies for BMI[7] (n=322,154) and AD[8] (n=103,066) (**Table E5**).

| Dataset | Sample size | AD cases/controls (prevalence %) | Females (%) | Mean [SD] age (years) | Mean [SD] BMI (kg/m²) |
|---|---|---|---|---|---|
| **UK Biobank** | 299,343 | 9,933 / 289,410 (3.3) | 158,103 (52.8) | 57 [8.0] | 27.4 [4.8] |
| **HUNT** | 18,048 | 1,775/ 16,273 (9.9) | 9,940 (55.1) | 53.7 [15.2] | 27.2 [4.4] |
| **BMI GWAS**[17] | 322,154 | - | - | - | 27.1 [4.6] |
| **AD GWAS**[19] | 103,066 | 18,900 / 84,166 (18.3) | - | - | - |

**Table E5. Descriptive statistics of datasets used in the study**. HUNT, Nord-Trøndelag Health Study; SD, standard deviation.

*Genotyping*

Genotyping of UK Biobank participants was performed with one of two arrays (Applied Biosystems™ UK BiLEVE Axiom™ Array (Affymetrix) and Applied Biosystems™ UK Biobank Axiom™ Array). Sample quality control (QC) measures included removing individuals who were duplicated and highly related (third degree or closer), had sex mismatches, as well as those identified to be outliers of heterozygosity and of non-European descent. Further details of the QC measures applied, and imputation performed have been described previously.[9-11]

Genotyping of the HUNT participants was performed with one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1 and UM HUNT Biobank v1.0). The genotypes from different arrays had QC performed separately and were reduced to a common set of variants across all arrays. Sample QC measures were similar to those applied to the UK Biobank. Related individuals were excluded from the analysis (n=30,256). Details of the genotyping, QC and imputation are described elsewhere.[12]

*Genetic instruments*

The genetic instrument for BMI comprised the 97 BMI-associated SNPs reported by the GIANT consortium (a meta-analysis of 125 GWAS studies with 339,224 individuals).[7] We note that this study included 1,334 individuals from the HUNT dataset in their analysis. The 97 SNPs were extracted from both UK Biobank and HUNT datasets and combined to create a separate standardised genetic risk score (GRS) for each dataset using the --score command in PLINK (version 1.9). The dosage of the effect allele for each SNP was weighted by the effect estimates reported for the European sex-combined analysis (n= 322,154) by Locke *et al*,[7] summed across all variants and divided by the total number of variants. The scores were standardized to have a mean of 0 and standard deviation of 1. One BMI-associated SNP, rs12016871, was not present within the UK Biobank and HUNT datasets, therefore rs9581854 was used as a highly correlated proxy ($r^2$ = 1.0). Of the 97 BMI SNPs, 22 are strongly associated with BMI in childhood[13] and since AD is a predominantly paediatric disease we used these SNPs as genetic instruments for BMI in childhood. The associations of BMI genetic instruments with BMI in UK Biobank and HUNT and associations of BMI genetic instruments with atopic dermatitis (AD) in UK Biobank and HUNT (using BMI variants reported by Locke *et al*. 2015) are available in GitHub (https://github.com/abudu-aggrey/Eczema_BMI_MR).

In addition, the BMI-associated SNPs most recently reported by Yengo *et al*[14] were used as an updated genetic instrument for BMI, to include novel BMI variants which may strengthen the genetic instrument. However, this study included individuals from the UK Biobank and was therefore not our preferred genetic instrument for the main analysis.

For the AD genetic instrument, 24 SNPs that had been reported within white European populations in the most recent AD GWAS (meta-analysis of 21,399 cases and 95,464 controls)[8] were used. This GWAS did not contain individuals from UK Biobank or HUNT (**Table E5**). The associated SNPs were extracted from UK Biobank and HUNT datasets and combined to create a standardized GRS for each dataset, weighted by the published effect estimates reported for European individuals (18,900 cases; 84,166 controls).[8] Within the HUNT dataset, the AD-associated SNP rs12153855 was not present and no suitable proxy ($r^2$ > 0.8) was found, therefore 23 SNPs were used to create the genetic instrument in the HUNT analysis.

The BMI GRS was strongly associated with BMI in both UK Biobank (Beta=0.64; 95% CI 0.63 to 0.66, F-statistic=7091, $R^2$=1.8%) and HUNT (Beta=0.66; 95% CI 0.60 to 0.72, F-statistic=422, $R^2$=2.3%). Likewise, a GRS of the childhood BMI SNPs was also strongly associated with BMI in UK Biobank (Beta=0.48; 95% CI 0.47 to 0.50, F-statistic=185, $R^2$=2.6%). The AD GRS was found to be a good predictor of AD in both UK Biobank (OR=1.26; 95% CI 1.23 to 1.28, F-statistic=2036, $R^2$=0.7%) and HUNT (OR=1.15; 95% CI 1.11 to 1.21, F-statistic=97, $R^2$=0.4%) datasets.

*MR: investigation of the effect of BMI on AD*

One-sample MR analysis was performed in the UK Biobank and HUNT datasets with the individuals' BMI SNPs, measured BMI and AD status (**Figure E5(a)**). The MR estimates from each SNP were meta-analysed assuming a random effects model, giving a single estimate for the analysis performed in each dataset. A random effects model was used to avoid over-precision of the causal estimate, and to allow for heterogeneity in the causal estimates being meta-analysed from the different genetic variants.

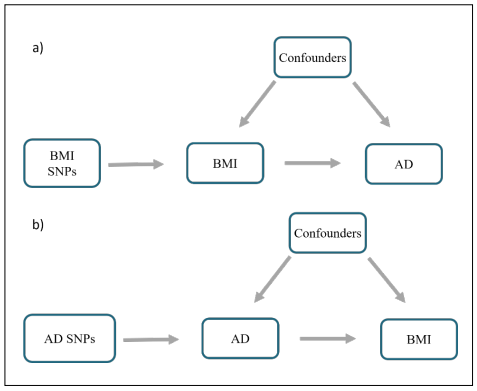


**Figure E5. Schematic representation of MR analyses.**

a) BMI SNPs were used as instrumental variables to investigate the causal effect of BMI upon AD.

b) AD SNPs were used as instrumental variables to investigate the causal effect of AD genetic risk of upon BMI. Arrows indicate MR assumptions where the instrumental variable is associated with the exposure, not associated with confounders, and only affects the outcome via the exposure. AD, atopic dermatitis; BMI, body mass index; SNP, single nucleotide polymorphism.

The MR analysis with the individual BMI SNPs was performed with the two-stage predictor substitution (TSPS) method.[15] The first stage involved regression of BMI upon individual BMI SNPs. The outcome (AD) was then regressed upon the fitted values from the first regression stage. As AD is a binary outcome, the first stage linear regression was restricted to control individuals, as recommended by Burgess *et al*.[16] Logistic regression was then performed in the second stage where the fitted values for the cases were predicted. The standard errors (SE) of these estimates were adjusted using the first term of the delta method expansion for the variance of a ratio, allowing for the uncertainty in the first regression stage to be considered.[16] Genetic principal components (as previously described[11, 12]) were included as covariates in the analysis to control for residual population structure. UK Biobank analysis also controlled for the platform used to genotype the samples. A similar protocol was followed in HUNT adjusting for the first four principal components and genotyping batch.

Two-sample MR analysis of published GWAS data was performed using the "TwoSampleMR" R package.[17] Estimates for the association between BMI and BMI SNPs in Europeans were taken from the GIANT BMI GWAS study published by Locke and colleagues.[7] Summary statistics from the most recent AD GWAS meta-analysis[8] were used to obtain estimates for the association of AD with the BMI SNPs in Europeans. The published BMI SNP estimates were based on an inverse normal transformation of BMI residuals on age and age-squared, as well as any necessary study-specific covariates. In unrelated individuals, residuals were calculated according to sex and case/control status and were sex-adjusted amongst related individuals. The causal estimates for the two-sample analysis were converted to raw BMI units (kg/m$^2$), assuming 4.6kg/m$^2$ to be the median BMI standard deviation.[7] The one-sample estimates obtained from UK Biobank and HUNT were meta-analysed assuming a fixed effect model. This was then meta-analysed with the two-sample estimate to obtain an overall causal estimate, assuming no between-method heterogeneity. This was performed using the genetic instrument of 97 BMI-associated SNPs, and separately for the instrument of 22 childhood BMI-associated SNPs. A separate two-sample MR analysis was performed in the same manner, using BMI SNP-BMI association estimates from the more recent BMI meta-analysis reported by Yengo and colleagues.[14]

*Asessment of confounders*

When investigating the association between the BMI GRS and potential confounders of BMI, some small associations with the confounders were seen (**Figures E6 and E7**). However, the magnitudes of these associations were minimal in comparison to the strength of association with BMI. The FTO variant alone also showed some effect on confounders, but it was much more strongly associated with measured BMI than potential confounders (**Figures E8 and E9**).

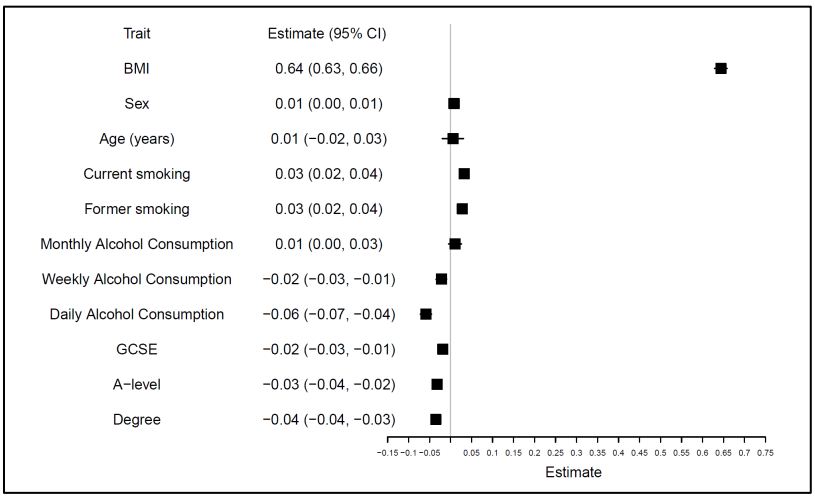


**Figure E6. Association of BMI genetic risk score with BMI (kg/m$^2$) and potential confounders in UK Biobank.** Estimates are given per 1 standard deviation increase in BMI GRS. A-level, Advanced level studies; CI, confidence interval; GCSE, General Certificate of Secondary Education; Monthly Alcohol Consumption was defined as frequency of "one to three times a month". For "sex", reference = Female".

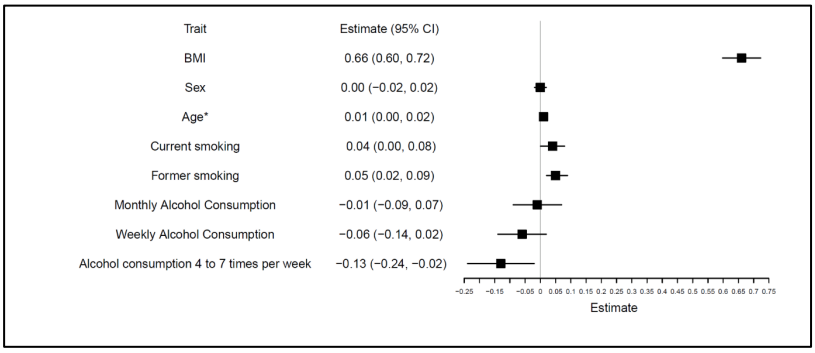


**Figure E7. Association of BMI GRS with BMI (kg/m$^2$) and potential confounders in HUNT.** Estimates are given per 1 standard deviation increase in BMI GRS. BMI, body mass index; CI, confidence interval.*age given per 10-year intervals. For "sex", reference = Female".

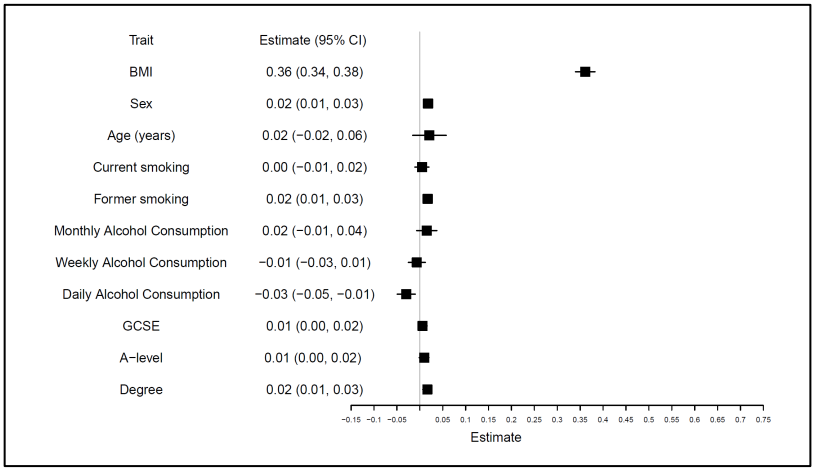


**Figure E8. Association of FTO SNP (rs1558902) with BMI (kg/m$^2$) and potential confounders in UK Biobank.** Estimates are given per 1 copy increase in effect allele (*A*). A-level, Advanced level studies; CI, confidence interval; GCSE, General Certificate of Secondary Education; Monthly Alcohol Consumption, defined as frequency of "one to three times a month". For "sex", reference = Female".

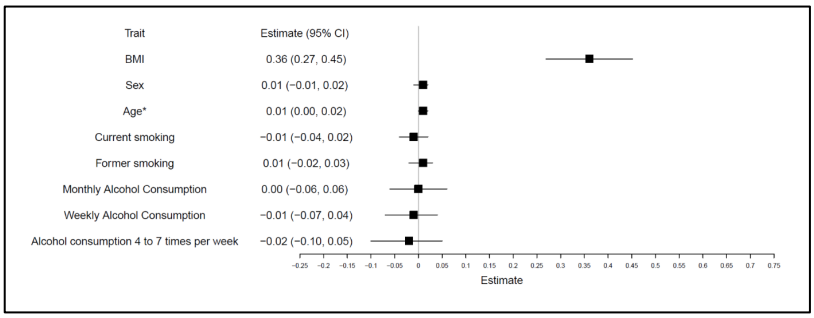


**Figure E9. Association of FTO SNP (rs1558902) with BMI (kg/m$^2$) and potential confounders in HUNT.** Estimates are given per 1 copy increase in effect allele (*A*). *age given per 10-year intervals. For "sex", reference = Female".

*Sensitivity analysis*

MR-Egger regression, weighted median analysis and the weighted mode-based estimate (MBE) were used to investigate potential horizontal pleiotropy. The strict definition of pleiotropy is when a SNP influences more than one trait.[18] In MR, vertical pleiotropy is assumed where the genetic instrument influences the exposure which in turn influences the outcome. However, SNPs that influence the exposure and the outcome through different pathways, known as horizonal pleiotropy, would violate the MR assumption that the instrumental variable has an effect on the outcome only via the exposure being investigated and could bias the causal estimate.[19] The weighted median method provides a valid causal estimate if at least 50% of the information in the MR analysis comes from valid instruments.[20]

Likewise, the weighted MBE also provides a valid causal estimate based on the assumption that the most frequent pleiotropy value is zero across the genetic instruments,[21] whilst the intercept from the MR-Egger regression analysis allows the size of any pleiotropic effect to be determined.[22] MR-Egger regression gives a valid causal estimate under the 'InSIDE' assumption, where each SNP-exposure effect is uncorrelated with the horizontal pleiotropic effect of the SNP.[22] We also used heterogeneity statistics to detect invalid instruments in MR that are due to the presence of pleiotropy.[23] As a proof-of-concept, one-sample MR analysis was performed using the *FTO* SNP alone (rs1558902) as a genetic instrument due to its strong association with BMI.[24, 25] The instrumental variables used in an MR analysis are assumed to be independent of confounders to avoid bias of the causal estimate. We therefore investigated the relationship between the BMI GRS, the *FTO* variant alone, and potential confounders of BMI by performing a simple regression of the confounder upon the BMI GRS and *FTO* variant.

*Reverse MR: investigating the effect of AD genetic risk on BMI*

In this reverse MR, we investigated the genetic liability of AD upon BMI (**Figure E5(b)**). One-sample MR analysis was performed separately in the UK Biobank and HUNT datasets using the two-stage least squares (TSLS) method with individual AD SNPs as genetic instruments. This analysis involves two regression stages where AD is first regressed upon the instrument (disease-associated SNPs), then the outcome (BMI) is regressed upon the fitted values from the first stage regression.[19] The final one-sample MR estimates from UK Biobank and HUNT were meta-analysed assuming a fixed effect model to give a single causal estimate (change in BMI per log odds of AD). To aid interpretation of the causal estimate, one-sample MR was also performed where genetic liability for AD was considered as a continuous variable, with values from "0" to "1" to give the difference in BMI between AD cases and controls with the "ivpack" R package.[26] Two-sample MR analysis was performed with the "TwoSampleMR" R package,[17] using summary results from GWAS studies for AD[8] and BMI.[7] The one- and two-sample MR estimates were meta-analysed using a fixed effect model to give an overall causal estimate. To aid interpretation, these estimates were multiplied by 0.693 to give the change in BMI per doubling odds of AD, as demonstrated by Gage *et al*.[27] Sensitivity analyses for the reverse MR were performed using MR-Egger regression, weighted median and weighted MBE analysis methods. A two-sample MR analysis was performed in the same manner, where AD SNP-BMI association estimates were extracted from the more recent BMI meta-analysis.[14]

*Analysis software*

All analyses were performed using R (www.r-project.org) unless otherwise stated. The code used to carry out these analyses is available on GitHub (https://github.com/abudu-aggrey/Eczema_BMI_MR).

***Results of MR analyses***

*Causal effect of BMI upon AD*

Similar causal estimates were found in UK Biobank (OR=1.03; 95% CI 1.00 to 1.06; *P*=0.10) and HUNT (OR=1.03; 95% CI 0.96 to 1.10; *P*=0.41). The estimate from the two-sample analysis with published GWAS data gave limited evidence of higher BMI increasing AD risk (OR=1.02; 95% CI 0.99 to 1.04; *P*=0.19).

Meta-analysis of the UK Biobank, HUNT and two-sample estimates showed evidence of a small causal effect, OR=1.02 (95% CI 1.00 to 1.04; *P*=0.03) (**Figure 1 in Letter**). This represents an increase in the odds of AD by ~2% for each 1 unit increase in BMI, or an increase in the risk of AD by approximately 11% for an increase in BMI of 5 units (OR per 5 units higher BMI = exp(Beta per 1 unit higher BMI * 5), for example, from 20 to 25kg/m$^2$. A similar causal estimate was found when restricting the BMI instrument to SNPs most strongly associated with childhood BMI (OR=1.04; 95% CI 1.01 to 1.07; *P*=0.01).

*Sensitivity analyses*

MR-Egger regression analysis showed little evidence of pleiotropy (UK Biobank intercept= 0.00; 95% CI -0.01 to 0.01; *P*=0.80, HUNT intercept=0.01; 95% CI -0.01 to 0.02; *P*=0.34) and the sensitivity analyses gave similar estimates (**Table E6, Figure E10**). There was also little evidence of heterogeneity among the individual effect estimates for each SNP in both datasets (UK Biobank Q=101.07, *P*=0.32; HUNT Q=100.04, *P*=0.37). MR analysis with the *FTO* SNP alone gave a slightly stronger estimate but with a wider confidence interval (OR=1.05; 95% CI 0.98 to 1.12; *P*=0.20) (**Figure E11**). Performing two-sample MR with the larger number of most recently published BMI SNP estimates (941 SNPs)[14] also gave evidence of a causal effect upon AD risk (OR=1.08; 95% CI 1.01 to 1.16; *P*=0.02).

*Effect of AD genetic risk upon BMI*

One-sample MR estimates in UK Biobank and HUNT gave little evidence that genetic risk of AD influences BMI (0.00kg/m$^2$ change in BMI per doubling odds of AD, 95% CI -0.06 to 0.06, *P*=0.94). Meta-analysis with the two-sample estimate also gave weak evidence of a very small causal effect (0.03 kg/m$^2$ change in BMI per doubling odds of AD, 95% CI -0.02 to 0.08, *P*=0.24). However, we note that the *FLG* loss-of-function variant (R501X/rs61816761) known to be strongly associated with AD[28] was not available in the two-sample analysis. There was little evidence of pleiotropy in the causal estimate for genetic risk of AD on BMI, and modest heterogeneity among the individual SNP effects (UK Biobank Q=66.51, *P*=4.15x10$^{-6}$; HUNT Q=24.10, *P*=0.34) (**Table E7, Figure E12**).

When performing two-sample MR with summary data for the most recently reported BMI SNPs,[14] the causal difference in BMI also gave very little evidence for BMI being influenced by genetic risk for AD, (0.02 kg/m$^2$ lower BMI in cases compared with controls, 95% CI -0.12 to 0.15, *P*=0.82). It should be noted, however, that summary statistics were not available for 5 of the 24 AD-associated SNPs in this analysis, including the *FLG* loss-of-function variant (R501X/rs61816761), thereby weakening the genetic instrument.

**Table E6. Sensitivity analyses for the causal effect of BMI upon AD**.

| Dataset | TSPS OR (95% CI) | IVW OR (95% CI) | MR-Egger OR (95% CI) | Weighted Median OR (95% CI) | Weighted MBE OR (95% CI) |
|---|---|---|---|---|---|
| UK Biobank | 1.03 (1.00, 1.06) | 1.03 (1.00, 1.06) | 1.03 (0.97, 1.10) | 1.02 (0.97, 1.07) | 1.02 (0.97, 1.08) |
| HUNT | 1.03 (0.96, 1.10) | 1.04 (0.97, 1.11) | 0.99 (0.88, 1.11) | 0.99 (0.89, 1.09) | 0.99 (0.82, 1.20) |

OR per 1 unit increase in BMI (kg/m$^2$); CI, confidence interval; IVW, inverse variance weighted analysis; MBE, mode-based estimate; OR, odds ratio; TSPS, two-stage predictor substitution.

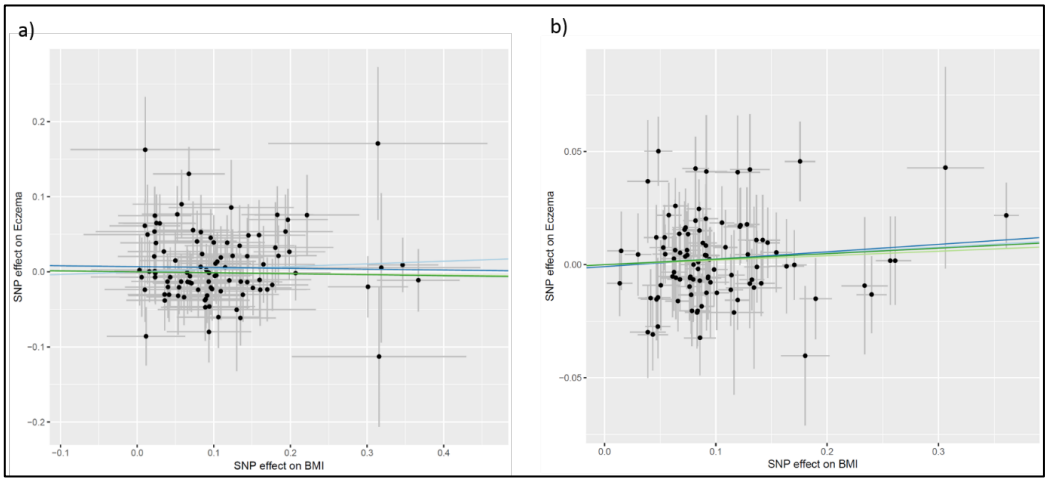


**Figure E10. Associations of BMI SNPs with BMI and AD within a) UK Biobank b) HUNT.** IVW, MR-Egger, weighted median and weighted mode estimates are indicated by the light blue, dark blue, light green, and dark green lines respectively.

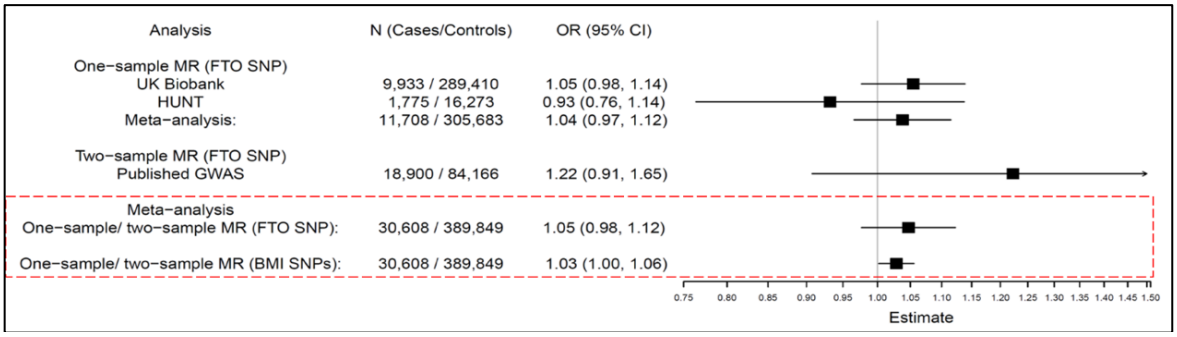


**Figure E11. Effect of FTO variant, rs1558902 upon AD.** Results from MR analysis using rs1558902 as an instrumental variable. These are compared with final estimates obtained when using all BMI SNPs as a genetic instrument. Estimates are given per 1 unit increase in BMI (kg/m$^2$).

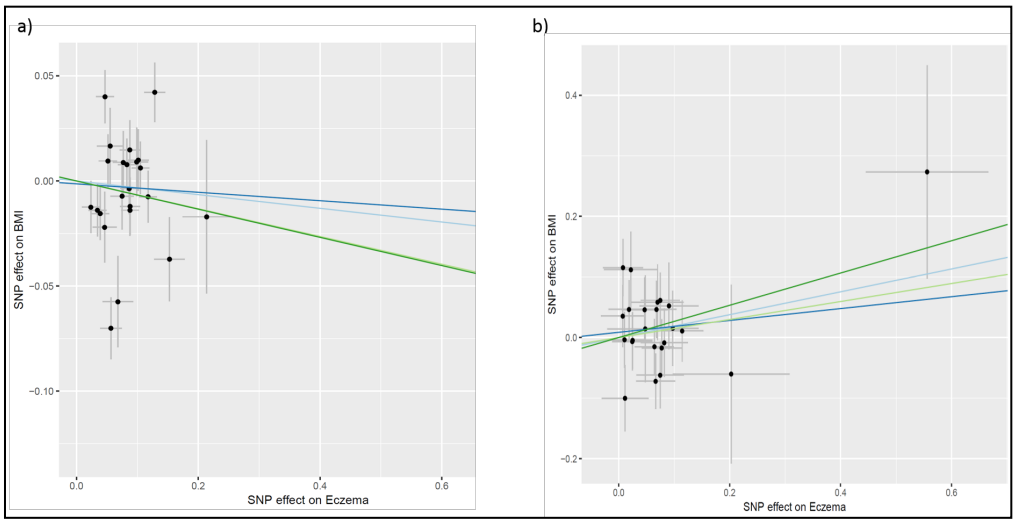


**Figure E12. Association of AD SNPs with AD and BMI within (a) UK Biobank and (b) HUNT.** IVW, MR-Egger, weighted median and weighted mode estimates are indicated by the light blue, dark blue, light green, and dark green lines respectively.

**Table E7. Sensitivity analyses for the causal effect of AD genetic risk upon BMI.**

| Dataset | TSLS estimate* (95% CI) | IVW estimate** (95% CI) | MR-Egger estimate (95% CI) | Weighted Median estimate (95% CI) | Weighted MBE (95% CI) |
|---|---|---|---|---|---|
| UK Biobank | -0.01 (-0.07, 0.05) | -0.10 (-0.44, 0.23) | -0.06 (-0.71, 0.59) | -0.21 (-0.51, 0.09) | -0.21 (-0.56, 0.13) |
| HUNT | 0.13 (-0.13, 0.39) | 0.60 (-0.44, 1.64) | 0.31 (-1.29, 1.91) | 0.47 (-1.01, 1.96) | 0.85 (-0.60, 2.30) |

Change in BMI (kg/m$^2$) per doubling odds of atopic dermatitis; CI, confidence interval; IVW, inverse variance weighted analysis; MBE, mode-based estimate; TSLS, two-staged least squares.

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