




# Atopic eczema and obesity: a population-based study

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## Summary

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K.A. reports and receives consulting fees from TARGET DERM, a company starting an atopic dermatitis disease registry, and receives grant funding (through her University) from Pfizer. L.S. is a trustee of the British Heart Foundation (BHF), and reports grants outside of the submitted work from Wellcome, the Medical Research Council, National Institute for Health Research, GSK, the BHF and Diabetes UK. S.M.L. reports grants from the Wellcome Trust, and received an Innovative Medicines Initiative BIOMAP Horizon 2020 grant during the conduct of the study. A.A., K.E.M., Y.S., A.M. and A.R. declare they have no conflicts of interest.

A.A. and K.E.M. contributed equally to the study and are joint first authors. S.M.L. had the original idea for the study. All authors were involved in the study design. K.M. undertook initial data management. A.A. undertook subsequent data management and the primary analysis and wrote the first draft. Y.S. provided advice on data management and analysis. All authors contributed to

**Background** Atopic eczema is a common chronic inflammatory skin disease. Research suggests an association between atopic eczema and obesity, with inconsistent evidence from European populations.

**Objectives** To explore the association between diagnosed atopic eczema and being overweight or obese, and whether increased atopic eczema severity was associated with higher body mass index.

**Methods** We undertook a cross-sectional analysis within a cohort of adults (matched by age, sex and general practice) with and without a diagnosis of atopic eczema. We used primary care (Clinical Practice Research Datalink Gold) and linked hospital admissions data (1998–2016). We used conditional logistic regression to compare the odds of being overweight or obese (adjusting for confounders and potential mediators) in those with atopic eczema (mild, moderate and severe, and all eczema) vs. those without.

**Results** We identified 441 746 people with atopic eczema, matched to 1 849 722 without. People with atopic eczema had slightly higher odds of being overweight or obese vs. those without [odds ratio (OR) 1.08, 95% confidence interval (CI) 1.07–1.09] after adjusting for age, asthma and socioeconomic deprivation. Adjusting for potential mediators (high-dose glucocorticoids, harmful alcohol use, anxiety, depression, smoking) had a minimal impact on effect estimates (OR 1.07, 95% CI 1.06–1.08). We saw no evidence that odds of being overweight or obese increased with increasing atopic eczema severity, and there was no association in people with severe eczema.

**Conclusions** We found evidence of a small overall association between atopic eczema and being overweight or obese. However, there was no association with obesity among those with the most severe eczema. Our findings are largely reassuring for this prevalent patient group who may already have an increased risk of cardiovascular disease.

### What is already known about this topic?

- Research from North America and Asia suggests that atopic eczema is associated with being overweight or obese; however, evidence from Europe is inconsistent.
- Atopic eczema symptoms, including chronic itch, may lead to sleep disturbance, anxiety and depression, which may contribute to being overweight or obese, through lifestyle exposures and inflammation.
- Only one small previous cross-sectional study has explored links between self-reported atopic eczema severity and obesity.

further drafts and approved the final manuscript.

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### What does this study add?

- We found evidence of a small association between diagnosed atopic eczema and being overweight or obese.
- However, in a large population-based study involving more than 2 million English adults we found no association between severe atopic eczema and being overweight or obese.
- Our findings are reassuring for patients and practitioners. Based on this study, we do not recommend any changes to clinical practice.

Atopic eczema is an increasingly common<sup>1</sup> chronic inflammatory skin condition affecting up to 10% of adults.<sup>2,3</sup> At the same time, obesity is a major global health challenge: 39% of adults are overweight and 13% are obese.<sup>4</sup> Obesity is a major modifiable risk factor for numerous health conditions including cardiovascular disease, cancer and diabetes.<sup>4</sup> Atopic eczema has also been linked to major adverse health outcomes including cardiovascular disease;<sup>5,6</sup> previous studies have proposed that increased prevalence of cardiovascular risk factors, such as being overweight or obese, may be an important contributory factor.<sup>7</sup> A meta-analysis reported an association between atopic eczema and being overweight or obese in North American and Asian studies, but no association in European populations.<sup>8</sup>

There are a number of potential explanations for an association between atopic eczema and obesity. The symptoms associated with atopic eczema could contribute to obesity; for example, chronic itch can lead to sleep disturbance,<sup>9,10</sup> which could lead to weight gain and increased cardiovascular risk.<sup>11,12</sup> People with atopic eczema may avoid physical exercise in order to avert the discomfort caused by sweating onto inflamed skin.<sup>13</sup> The role of the gut microbiome (the collective genomes of gut microbes) may also be relevant; however, its role in obesity and in atopic eczema is not yet clearly defined.<sup>14,15</sup> In addition, treatment with glucocorticoids, or the underlying systemic inflammation from atopic eczema itself, could also lead to weight gain.<sup>7</sup> Alternatively, factors associated with obesity could contribute to atopic eczema, including increased transepidermal water loss,<sup>16</sup> and proinflammatory changes.<sup>17,18</sup>

Existing research has often been limited by using self-reported rather than physician-diagnosed atopic eczema, and has lacked important detail on how the association with being overweight or obese varies by atopic eczema severity.<sup>8</sup> Understanding how the relationship between atopic eczema and being overweight or obese changes with atopic eczema severity could inform our understanding of underlying mechanisms. We aimed to explore the association between diagnosed atopic eczema and being overweight or obese, and investigate the effect of increasing atopic eczema severity on being overweight or obese.

## Patients and methods

### Study design and setting

We undertook a cross-sectional analysis of a cohort of adults, with and without atopic eczema, identified in the Clinical Practice Research Datalink Gold (CPRD Gold). CPRD contains high-quality anonymized electronic health record data from over 650 UK general practices.<sup>19</sup> As the majority of the UK population are registered with a general practitioner (GP), CPRD provides a broadly representative population.<sup>19</sup>

GPs in England act as the gateway to health care. Most people with atopic eczema in England are managed in primary care by GPs,<sup>20</sup> although individuals with moderate and severe atopic eczema may be jointly managed with secondary care by dermatologists. We also used linked hospital admissions data from Hospital Episode Statistics (HES). HES includes data on all National Health Service-funded hospital admissions in England.<sup>21</sup> Seventy-five per cent of English practices contributing to CPRD are eligible for linkage with HES.<sup>19</sup>

The study was approved by the London School of Hygiene and Tropical Medicine Research Ethics Committee (Reference 11961-2) and by the CPRD Independent Scientific Advisory Committee (Protocol Number: 16\_100RA).

### Study population

We identified a matched cohort of adults (aged 18 years and over), with and without a diagnosis of atopic eczema, with a valid body mass index (BMI) measure recorded in primary care. Individuals eligible for study inclusion were those registered with CPRD practices eligible for linkage with HES data. Individuals were required to have at least 12 months of registration (to allow adequate timing for recording of baseline health status), and to have at least one record of BMI (full eligibility criteria are available in Appendix S1; see Supporting Information). Figure 1 shows a visual representation of cohort entry and exit.

We identified all individuals with atopic eczema based on a validated algorithm requiring primary or secondary care records of at least one diagnostic atopic eczema code and at

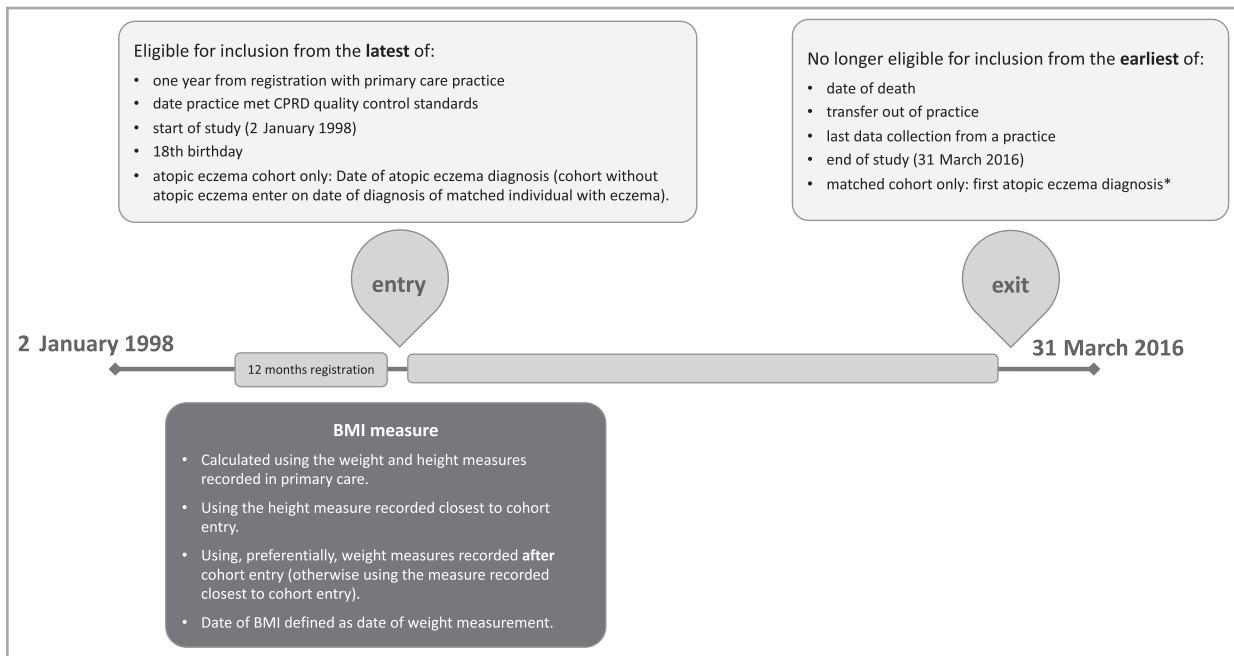


Figure 1 Visual representation of cohort entry and exit, and calculation of body mass index (BMI,  $\text{kg m}^{-2}$ )

least two atopic eczema therapies (including prescribing and phototherapy) recorded on separate days (Appendix S1).<sup>22</sup> We defined the date of atopic eczema diagnosis as the date at which the individual fulfilled the full atopic eczema algorithm (latest of atopic eczema diagnosis code or second atopic eczema therapy record).

Individuals with atopic eczema were matched (without replacement) with up to five individuals without atopic eczema on age, sex and GP practice, in calendar date order (i.e. individuals in the matched cohort were assigned first to those with earliest cohort entry to avoid time-related bias). We used a 15-year age-matching window to minimize potential selection bias introduced by excluding unmatched individuals (we adjusted for age to account for this wide window).

## Outcome

We defined individuals as being overweight or obese if their BMI was  $25 \text{ kg m}^{-2}$  or more based on the World Health Organization definition (overweight:  $\text{BMI} \geq 25 \text{ kg m}^{-2}$  and  $< 30 \text{ kg m}^{-2}$ ; obese:  $\geq 30 \text{ kg m}^{-2}$ ).<sup>4</sup> We compared overweight and obese individuals with those who were underweight or normal weight (underweight:  $< 18.5 \text{ kg m}^{-2}$ ; normal weight:  $\geq 18.5 \text{ kg m}^{-2}$  and  $< 25 \text{ kg m}^{-2}$ ) (further details in Figure 1 and Appendix S1).

## Covariates

We used a directed acyclic graph (Appendix S2; see Supporting Information) to visualize the relationships between atopic eczema (exposure), BMI (outcome), and potential

confounders or mediators.<sup>23</sup> We considered the following as potential confounders of the association between atopic eczema and increased BMI: age, sex, socioeconomic deprivation and asthma.

We used quintiles of index of multiple deprivation (IMD) to capture socioeconomic deprivation.<sup>24</sup> We defined asthma as any diagnostic code for asthma recorded in primary or secondary care on or before cohort entry. We considered the following as possible mediators: smoking,<sup>25</sup> depression,<sup>26</sup> anxiety,<sup>27</sup> harmful alcohol use,<sup>28</sup> and high-dose oral glucocorticoid use. To fulfil our depression or anxiety definitions, we required that individuals had at least one diagnostic code for anxiety (generalized anxiety disorder or panic disorder) or depression in either primary or secondary care on or before cohort entry date. We defined high-dose oral glucocorticoid use as a prescription for an oral glucocorticoid equivalent to 20 mg or more per day of prednisolone prescribed on or before cohort entry date.

Full details of all covariate definitions are in Appendix S1. We also considered ethnicity as a potential confounder,<sup>3</sup> but only adjusted for it in a sensitivity analysis (Appendix S3, sensitivity analysis; see Supporting Information) restricting to those entering the cohort from 2006 when ethnicity data were more complete.<sup>29</sup> Complete morbidity code lists for all variables are available to download at <https://doi.org/10.17037/DATA.00000918>.

## Statistical analyses

We undertook all analyses using Stata Statistical Software, Release 15.1 (StataCorp LLC, College Station, TX, USA).

## Main analysis

We used logistic regression, conditional on matched set, to estimate odds ratios (ORs) [95% confidence intervals (CIs)] comparing the odds of being overweight or obese between those with atopic eczema and those without. We initially fitted minimally adjusted models adjusting explicitly for age (in 5-year bands), and implicitly for sex and GP practice (through matching). We then additionally adjusted for potential confounders (IMD and asthma). Finally, we further adjusted for potential mediators of the relationship between atopic eczema and being overweight or obese (anxiety, depression, harmful alcohol use, high-dose oral glucocorticoid use and smoking status). Smoking data were missing for some individuals, so we performed a complete-case analysis, preserving matching by further excluding any individuals who were unmatched as a result.

## Sensitivity analyses

We tested the robustness of our findings by repeating the main analysis in a series of sensitivity analyses: (i) excluding underweight individuals, whose association with atopic eczema may be qualitatively different from normal-weight individuals, masking an association between atopic eczema and being overweight or obese; (ii) excluding overweight individuals, as atopic eczema may be more strongly associated with being obese than with being overweight; (iii) restricting cohort entry to 2004, when BMI was more completely recorded, to minimize potential selection bias; (iv) excluding women of childbearing age (18–45 years) who may have a recorded weight increase due to pregnancy; and (v) adjusting for possible confounding effects of ethnicity, restricting to individuals entering the cohort from 2006 when ethnicity was more completely recorded (Appendix S3, sensitivity analysis).

## Secondary analyses

We conducted two secondary analyses to investigate: (i) the association between atopic eczema severity and BMI; and (ii) whether the association between atopic eczema and BMI was modified by sex (studies suggest the association is stronger in women than men<sup>30</sup>).

We defined atopic eczema severity using records for atopic eczema therapies and referral with atopic eczema to a dermatologist. Individuals with atopic eczema were considered to have mild atopic eczema by default; moderate eczema if prescribed two potent topical steroids (within one year) or a topical calcineurin inhibitor; or severe eczema if given phototherapy, systemic treatment, or referred to a dermatologist (details in Appendix S1). We defined atopic eczema severity using all information recorded on or before cohort entry. We compared the odds of being overweight/obese in individuals with mild, moderate and severe atopic eczema with those who had no atopic eczema.

## Results

We identified a cohort of 441 746 adults with atopic eczema, matched to 1 849 722 without (Figure 2). Individuals with and without atopic eczema had similar smoking status and level of socioeconomic deprivation (Table 1). People with atopic eczema were more likely to have an asthma diagnosis than were individuals without atopic eczema (23.4% vs. 12.4%). The proportion of individuals with missing smoking status was similar for individuals with and without atopic eczema. Individuals excluded, due to missing or improbable BMI information, were likely to be younger and have less follow-up time than those included in the study cohort (Appendix S3, missing data; see Supporting Information).

The proportion of people who were overweight or obese was similar in those with atopic eczema (56.3%) and without (55.3%). After adjusting for age, people with atopic eczema had 10% higher odds (OR 1.10, 95% CI 1.10–1.11) of being overweight or obese than those without atopic eczema. The association between atopic eczema and increased BMI attenuated slightly (although 95% CIs overlapped) after additionally adjusting for asthma and socioeconomic deprivation (OR 1.08, 95% CI 1.07–1.09). Further adjusting for potential mediators (high-dose oral glucocorticoid use, harmful alcohol use, anxiety, depression and smoking) made little difference to the point estimate (OR 1.07, 95% CI 1.06–1.08) (Table 2).

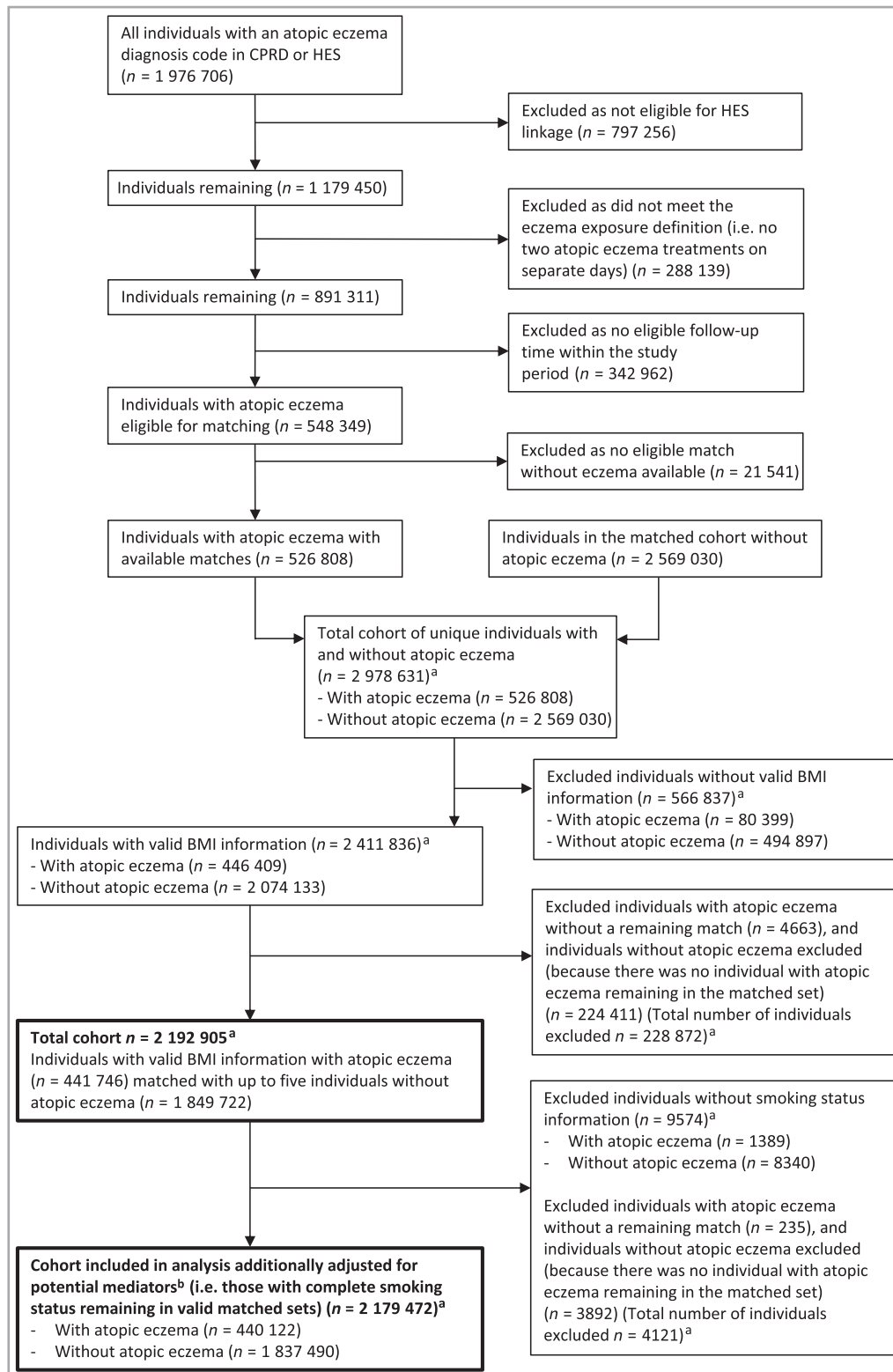
## Sensitivity analyses

The results of our sensitivity analyses were broadly similar to the results of the main analysis and did not change our conclusions (Appendix S3, sensitivity analysis).

## Secondary analyses

After adjusting for age, asthma and socioeconomic deprivation, compared with individuals without atopic eczema: (i) in people with mild atopic eczema we found evidence of a small increased risk of being overweight or obese (OR 1.06, 95% CI 1.05–1.07); (ii) having moderate atopic eczema was associated with 14% higher odds (OR 1.14, 95% CI 1.13–1.16) of being overweight or obese; but (iii) there was no evidence of an association between severe atopic eczema and being overweight or obese (OR 1.00, 95% CI 0.96–1.03) [Figure 3; Appendix S3, association between atopic eczema severity and being overweight or obese (see Supporting Information)]. There was strong evidence (Wald test  $P < 0.001$ ) against homogeneity in the effect sizes for mild, moderate and severe atopic eczema compared with no atopic eczema.

We found evidence ( $P < 0.001$ ) that sex modified the association between atopic eczema and increased BMI; however, the difference in estimates was very small. After adjusting for age, socioeconomic deprivation and asthma, women with atopic eczema were slightly more likely than men with atopic



**Figure 2** Flowchart illustrating identification of study participants. CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; BMI, body mass index ( $\text{kg m}^{-2}$ ). <sup>a</sup>Numbers of individuals with and without eczema do not necessarily sum to the total number of individuals included, as individuals with eczema could be included in the matched comparison cohort up until the date of their first eczema diagnosis. <sup>b</sup>Cohort used in model adjusted for potential mediators (anxiety, depression, harmful alcohol use, high-dose oral glucocorticoid use and smoking status).

**Table 1** Characteristics of individuals with and without atopic eczema

Characteristic	Without atopic eczema n = 1 849 722	With atopic eczema n = 441 746
Follow-up (years), median (IQR)	5 (2.0–9.7)	5.5 (2.3–10.3)
Age on cohort entry (years), median (IQR)	46.6 (32.1–62.7)	45.7 (30.3–63.6)
Female	1 167 224 (63.1)	273 322 (61.9)
Index of multiple deprivation		
1 (least deprived)	442 288 (23.9)	105 746 (23.9)
2	425 555 (23.0)	101 411 (23.0)
3	366 117 (19.8)	86 776 (19.6)
4	352 822 (19.1)	84 646 (19.2)
5 (most deprived)	262 940 (14.2)	63 170 (14.3)
Asthma	229 217 (12.4)	103 482 (23.4)
Smoking status		
Current or ex-smoking	887 579 (48.0)	220 308 (49.9)
Never smoking	953 803 (51.6)	220 049 (49.8)
Missing smoking data	8340 (0.5)	1389 (0.3)
BMI (kg m <sup>-2</sup> )		
Underweight (< 18.5)	53 203 (2.9)	12 668 (2.9)
Normal (18.5–24.9)	767 939 (41.5)	178 507 (40.4)
Overweight (25.0–29.9)	623 207 (33.7)	147 071 (33.3)
Obese (≥ 30.0)	405 373 (21.9)	103 500 (23.4)

Numbers are n (%) unless otherwise stated. IQR, interquartile range; BMI, body mass index.

eczema to be overweight or obese (women: OR 1.09, 95% CI 1.08–1.10; men: OR 1.06, 95% CI 1.04–1.07).

## Discussion

In our cross-sectional analysis of a large, population-based cohort, we found a small association between diagnosed atopic eczema and being overweight or obese. However, there was no association between severe atopic eczema and being overweight or obese, and there was evidence against homogeneity by atopic eczema severity. Over half of our study population, regardless of atopic eczema status, were overweight or obese.

Our study is the first to examine the association between physician-diagnosed atopic eczema and being overweight or obese in a large population-based European study. A meta-analysis looking at adult atopic eczema and being overweight or obese estimated a pooled OR of 1.29 (95% CI 1.05–1.59), and while our point estimate was smaller (1.07, 95% CI 1.06–1.08) it was within the confidence limits of the meta-analysis.<sup>8</sup> However, after stratifying by region, the meta-analysis found no evidence of an association in European studies.<sup>8</sup>

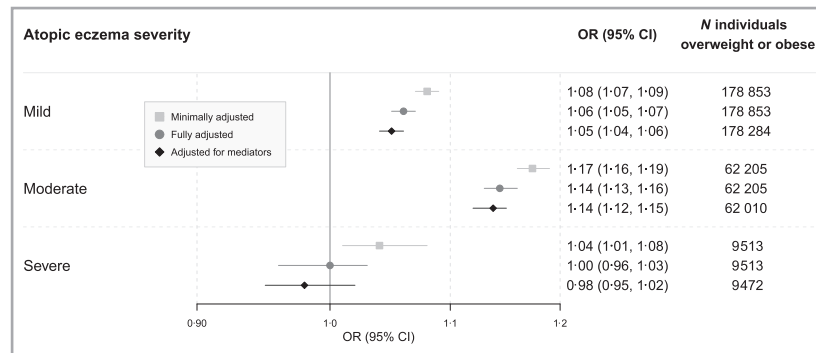
Our results are consistent with a single US study that assessed the association with obesity by disease severity.<sup>31</sup> While the previous US study of severity was based on self-reported eczema, the authors found results consistent with ours,

**Table 2** Association between atopic eczema and being overweight/obese [all models implicitly adjusted for sex and general practice due to matching]

	Models implicitly adjusted for sex and general practice (due to matching)				Model additionally adjusted for potential mediators (high-dose glucocorticoids, harmful alcohol use, anxiety, depression and smoking) <sup>a</sup>		
	Number of participants	Number of overweight or obese participants	OR (95% CI) adjusted for age	OR (95% CI) additionally adjusted for IMD and asthma	Number of participants	Number of overweight or obese participants	OR (95% CI)
No atopic eczema	1 849 722	1 028 580	1.00 (ref)	1.00 (ref)	1 837 490	1 022 881	1.00 (ref)
Atopic eczema	441 746	250 571	1.10 (1.10–1.11)	1.08 (1.07–1.09)	440 122	249 766	1.07 (1.06–1.08)

OR, odds ratio; CI, confidence interval; IMD, index of multiple deprivation. <sup>a</sup>Restricted to individuals with smoking status available and in valid matched sets (i.e. including at least one individual with atopic eczema and one without).





**Figure 3** Association between atopic eczema and being overweight or obese, by severity of atopic eczema compared with people without atopic eczema. All models are implicitly adjusted for sex and general practice due to matching. Minimally adjusted: adjusted for age; fully adjusted: adjusted for age, socioeconomic deprivation, asthma. Model additionally adjusted for potential mediators: adjusted for age, socioeconomic deprivation, asthma, high-dose oral glucocorticoid use, harmful alcohol use, anxiety, depression and smoking. OR, odds ratio; CI, confidence interval

where the strongest association was seen between moderate atopic eczema and obesity, and no association between severe atopic eczema and raised BMI,<sup>31</sup> suggesting that this unusual pattern of association may be consistent in both English and US populations. We saw a slightly stronger association between atopic eczema and being overweight or obese in women than men. While the difference in effect size was small and unlikely to be clinically significant, this finding is consistent with findings from other studies.<sup>30,32,33</sup> A potential explanation may be that women have a higher proportion of body fat than men.

While the magnitude of association seen in this study was small, there are a number of potential mechanisms for an association between atopic eczema and obesity. Obesity is a proinflammatory state, and atopic eczema is a chronic systemic inflammatory disease.<sup>34</sup> There may be behavioural changes related to atopic eczema, such as a lack of physical activity due to discomfort from sweating onto inflamed skin, or impaired quality of life and sleep problems.<sup>9</sup> There is also an association between atopic eczema and other factors associated with increased weight including high-dose oral glucocorticoid use, anxiety and depression,<sup>35</sup> and increased alcohol use,<sup>28</sup> although additionally adjusting for these made little difference to the point estimate, suggesting that these mediators had little effect on the relationship between atopic eczema and overweight or obesity. Asthma (a common disease often comorbid with atopic eczema) is associated with obesity, and this association has been found to be stronger in women.<sup>36–38</sup> Adjusting for asthma in our analysis only slightly attenuated the magnitude of association, suggesting that the small association between atopic eczema and being overweight or obese is independent of asthma comorbidity.

It is possible that raised BMI may predispose to atopic eczema. Adipose tissue is an endocrine organ, and leptin or oestrogen (found in higher concentrations in women)<sup>39</sup> may modulate the immune profile towards T-helper 2 (cells that help regulate the immune response) dominance,<sup>40</sup> an immunoprofile seen in atopic eczema.<sup>41</sup> Obesity itself may reduce the epidermal barrier function due to increased

sweating and blood pressure,<sup>16</sup> increased transepidermal water loss and changes to cutaneous lipid profiles.<sup>42</sup> A recent Mendelian randomization study supports this ‘reverse directionality’ of causation: increasing BMI was found to have a small causal association with atopic eczema; however, there was weak evidence that atopic eczema conferred a greater risk of raised BMI.<sup>43</sup> Similar results have been found in psoriasis (a distinct inflammatory skin condition).<sup>44</sup> Therefore, it is possible that the relationship between atopic eczema and obesity is bidirectional.

Our findings of the lack of dose–response relationship for the association between eczema severity and BMI were consistent with those of another study in a different population, using different methodology. This may suggest that the relationship is not causal, or is nonlinear. One explanation for the unusual relationship might be that people with severe atopic eczema may have a tendency towards food avoidance – secondary to real or perceived food allergy – leading to weight loss.<sup>45</sup> Finally, atopic eczema is a heterogeneous disease, and different subtypes may have variation in their underlying mechanisms and effect on weight.<sup>46</sup> The possibility of a nonlinear relationship between atopic eczema and obesity should be tested with further research using BMI as a continuous variable.

Our study has a number of strengths. We used a validated algorithm to identify atopic eczema.<sup>22</sup> Our atopic eczema and BMI definitions were physician diagnosed, rather than self-reported, avoiding bias introduced by self-report. We were also able to explore the effect of atopic eczema severity. Our study was population based, increasing the generalizability of our results. Our large sample size allowed us to calculate effect sizes with precision. At the same time, our study also had limitations. We were unable to provide information on temporality due to our cross-sectional design. However, in order to account for temporality as far as possible within the cross-sectional design, we selected covariates if they preceded cohort entry, and preferentially took weight measurements close to cohort entry. We considered physical activity, and food allergy or food avoidance, to be potential mediating factors; however,

as these could not be reliably captured in CPRD, we could not account for them. Similarly, we could not capture undiagnosed, misdiagnosed or unrecorded atopic eczema. There may be bias in our estimates if individuals who were excluded from our analyses due to missing BMI measurements were systematically more or less likely to be overweight/obese and to have atopic eczema than the individuals who were included. However, in a sensitivity analysis – restricting to more recent data when BMI recording was more complete – our results were unchanged, providing some assurance against bias due to missing BMI data.

In conclusion, this large, population-based study suggests a small association between atopic eczema and being overweight or obese. In a secondary analysis, we found no association between the most severe atopic eczema and being overweight or obese. The underlying mechanism for this small association remains unclear. As previous studies have reported that people with severe atopic eczema are already at higher risk of cardiovascular disease,<sup>5,6</sup> our findings are largely reassuring for patients and practitioners.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix S1** Variable definitions.

**Appendix S2** Directed acyclic graph.

**Appendix S3** Missing data; association between atopic eczema and being overweight or obese; and sensitivity analyses.