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## **Long-term effect of asthma on the development of obesity among adults: an international cohort study, ECRHS**

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## **KEY MESSAGES**

- **What is the key question?**

Is asthma a risk factor for the development of obesity in adults?

- **What is the bottom line?**

Asthmatics, particularly those who were non-atopic, had longer disease duration or were on oral corticosteroids, were at a higher risk of developing obesity later in life. This association was not mediated by physical activity.

- **Why read on?**

Although an association between obesity and asthma has been well established, whether asthma can relate to increased risk of future obesity has been only studied in children. Understanding the link between asthma and obesity is key for a proper asthma management.

## ABSTRACT

**Introduction:** Obesity is a known risk factor for asthma. Although some evidence showed asthma causing obesity in children, the link between asthma and obesity has not been investigated in adults.

**Methods:** We used data from the European Community Respiratory Health Survey (ECRHS), a cohort study in 11 European countries and Australia in 3 waves between 1990 and 2014, at intervals of approximately 10 years. We considered two study periods: from ECRHS I ( $t$ ) to ECRHS II ( $t+1$ ), and from ECRHS II ( $t$ ) to ECRHS III ( $t+1$ ). We excluded obese (BMI  $\geq 30$ kg/m<sup>2</sup>) individuals at visit  $t$ . The relative risk (RR) of obesity at  $t+1$  associated with asthma at  $t$  was estimated by multivariable modified Poisson regression (lag) with repeated measurements. Additionally, we examined the association of atopy and asthma medication on the development of obesity.

**Results:** We included 7,576 participants in the period ECRHS I-II (51.5% female, mean (SD) age of 34 (7) years), and 4,976 in ECRHS II-III (51.3% female, 42 (8) years). 9% of participants became obese in ECRHS I-II and 15% in ECRHS II-III. The risk of developing obesity was higher among asthmatics than non-asthmatics (RR: 1.22, 95%CI: 1.07 to 1.38), and particularly higher among non-atopic than atopic (1.47; 1.17 to 1.86 vs 1.04; 0.86 to 1.27), those with longer disease duration (1.32; 1.10 to 1.59 in  $>20$  years vs 1.12; 0.87 to 1.43 in  $\leq 20$  years), and those on oral corticosteroids (1.99; 1.26 to 3.15 vs 1.15; 1.03 to 1.28). Physical activity was not a mediator of this association.

**Conclusion:** This is the first study showing that adult asthmatics have a higher risk of developing obesity than non-asthmatics, particularly those non-atopic, of longer disease duration or on oral corticosteroids.

**Keywords:** Asthma, ECRHS, Obesity, Oral corticosteroids, Physical activity

## INTRODUCTION

Several studies demonstrating the co-existence of obesity and asthma across the world suggest the presence of common aetiological factors between these conditions.[1-5] Asthma and obesity share some common socioeconomic, behavioural, and environmental risk factors, all of which could trigger the expression of genes, leading to the development of either of these diseases. Previous studies focussed mainly on the mechanisms by which obesity could lead to asthma. Several obesity-associated biological phenomena have been proposed, such as by altering the lung compliance (causing airflow limitation), increasing the synthesis of immune-modulators, affecting the sympathetic nervous system, or by modulating gene function.[1, 2] The inverse relationship, i.e., whether asthma is a risk factor for later obesity had not received much attention until recently.

In a longitudinal cohort study of kindergarten and first-grade children, Chen and colleagues (2017) observed that the non-obese children who were diagnosed with asthma during the recruitment phase were at increased risk of developing obesity during the 10-years follow up.[6] This was confirmed in a pooled analysis of 18 European cohorts associating physician diagnosed asthma at 3-4 years with incident obesity at 8 years, the risk being higher among children with active asthma symptoms.[7] Another recent study demonstrated a link between high peak flow variability in childhood and a steeper increase of body mass index (BMI) in adulthood.[8] Despite studies on children and young adolescents, whether and to what extent asthma increased the risk for subsequent obesity among adults remained unclear. Asthma in adults may be causally and aetiologically more complex than childhood asthma (which is predominantly allergic asthma), therefore, the magnitude of the asthma-obesity risk is likely to be different in adults.

In line with the previously reported observations, we hypothesized that asthma could be a risk factor for obesity at a later stage of life. Therefore, we aimed to investigate the occurrence of obesity attributable to asthma in participants of the European Community Respiratory Health Survey (ECRHS) over two periods of 10 years.



## METHODS

### Design and participants

ECRHS is a population-based cohort study initiated in 1990-94 (ECRHS-I) with over 18,000 participants aged between 20 and 44 years from 30 centres in 14 countries, which had two follow-up rounds at approximately 10-year intervals (ECRHS-II in 1999-2003 and ECRHS-III in 2010-2014). In the recruitment phase, a postal questionnaire was sent containing items about asthma symptoms and exacerbation history in the last 12 months, current medication, and allergic conditions such as nasal symptoms and hay fever. From those who responded to the postal questionnaire, participants were either selected from a random sample or a symptomatic sample and were invited for more detailed investigation that included an interviewer-administered questionnaire and lung function testing.[9, 10] The questionnaires and clinical investigations were repeated in the next follow-ups (ECRHS-II and III).

The design and selection of participants of the present study are presented in **Figure 1**. We considered two study periods: from ECRHS I ( $t$ ) to ECRHS II ( $t+1$ ), and from ECRHS II ( $t$ ) to ECRHS III ( $t+1$ ). At each period we classified the participants as “no asthma” or “current asthma” (see definitions below). To study only incident obesity, we excluded individuals who were obese (BMI  $\geq 30\text{kg/m}^2$ ) at visit  $t$ . To avoid misclassification in the definition of the ‘current asthma’ and ‘no asthma’ groups, we excluded participants with inactive asthma (i.e. self-reported doctor diagnosed asthma, with no respiratory symptoms within the last 12 months). We finally excluded subjects with missing asthma or obesity information at either  $t$  or  $t+1$ , giving a total of 8,716 participants from 26 centres of 11 European countries and Australia. Ethical approval of the study was obtained from the ethical review boards or committees of the respective centres. All participants provided signed informed consent. Detailed information about the ethical approval, informed consent and data management were described elsewhere.[10]

- Figure 1

### **Definition of asthma-related variables**

Asthma-related information was collected at each survey. We defined current asthma as giving a positive answer to the questions “Have you ever had asthma?” and “Was this confirmed by a doctor?”, and having reported at least one of the following in the last 12 months: waking up by an attack of shortness of breath, any asthma attack, or use of asthma medications.[11-13] Asthma duration at  $t$  was derived as the number of years between age at  $t$  and reported age at first asthma onset. Atopy was defined as a serum specific IgE antibody concentration of  $\geq 0.35$  kU<sub>A</sub>/L to at least one of four common allergens (house dust mite, cat, timothy grass or *Cladosporium herbarum*), as defined previously.[14] We also obtained information on asthma drug treatment from the questions “Have you used any pills, capsules, tablets or medicines, other than inhaled medicines, to help your breathing at any time in the last 12 months?”, and defined whether each patient took inhaled (ICS) oral corticosteroids (OCS) or both during the last 12 months. Only at ECRHS II, information was collected on whether OCS were used continuously, for a short-course, or as rescue medication. The modified Medical Research Council (mMRC) Dyspnoea Scale was used to define dyspnoea (considered if they had mMRC grade  $\geq 2$ ).[15]

### **Obesity**

Height and weight of all participants were measured by physical examination during the clinical visit at each survey. BMI was calculated as weight in kilograms divided by the square of height in metres. Obesity was defined as  $BMI \geq 30$  kg/m<sup>2</sup>. [16]

### **Other relevant information**

At each study wave, we collected data on socio demographic and other clinical factors using questionnaires. These included sex, age, education (age at which the participants finished their formal education) and smoking status (never, former and current) and intensity (pack-years). Information about physical activity of the participants was obtained at ECRHS-II and III from a self-completed questionnaire in which they were asked about the weekly frequency and duration of vigorous physical activity.[17-19] Those who exercised at least two times a week for at least 1 hour were considered physically active.

## Statistical analyses

Relative risks (RR) and 95% confidence intervals (CIs) for the association of current asthma, asthma with atopy, asthma duration, and asthma with medication (ICS, OCS or both), with new obesity onset were estimated using modified Poisson regression for repeated measures with time of follow-up as offset.[20] Exposure was the asthma status at the survey time  $t$  (lag1) and outcome was obesity at subsequent time  $t+1$ . Therefore, participants could contribute with one or two observations, i.e., from ECRHS-I to ECRHS-II and/or from ECRHS-II to ECRHS-III (**Figure 1**). Multivariate models were fitted after testing the following potential confounders: education, sex, age, smoking status, and physical activity (between ECRHS-II and III only). Only those variables associated (i.e., p-value <0.05) both with asthma and obesity were retained. Hence, the final models were adjusted for age, sex, and smoking status at time  $t$ . Subjects nested in centre were included as random effects to account for the repeated data design.

Models were presented overall and separately by sex. We performed meta-analysis to determine if there was any heterogeneity between the participating countries and between centres.

Two secondary analyses were performed: (1) to determine if physical activity could be a mediator in the asthma-obesity association, we tested 3 paths separately: physical activity at ECRHS-II mediating the relationship between asthma at ECRHS-I and obesity at ECRHS-II (path 1), physical activity at ECRHS-II mediating the relationship between asthma at ECRHS-I and obesity at ECRHS-II (path 2), and physical activity at ECRHS-III mediating the relationship between asthma at ECRHS-II and obesity at ECRHS-III (path 3); and (2) to estimate the impact of smoking cessation on the association between asthma and new obesity onset, we stratified our models by active smokers (at time  $t$ ), smokers who quit during the study (between ECRHS-I and II, and ECRHS-II and III), and never smokers.

Some sensitivity analyses were performed to check the robustness of our results. We repeated our analyses: (1) excluding those who did not take part in all three ECRHS waves; (2) excluding participants who reported avoiding physical activity because of respiratory symptoms; (3) excluding those who reported dyspnoea at time  $t$ ; (4) defining current asthma as the a self-report

of doctor's diagnosis and at least one of the following within the last 12 months: waking up by an attack of shortness of breath, any asthma attack, use of asthma medications, wheeze, shortness of breath, waking up with chest tightness or attack of cough; and (5) using BMI change between  $t$  and  $t+1$  as the outcome variable in linear mixed regression. All analyses were performed in STATA (version 12.1, STATA Corp. College Station, Texas, USA).

## RESULTS

Distribution of the participants included in this analysis is presented in **Table 1**. We studied 7,576 participants in the period ECRHS I-II (51.5% female, mean (SD) age of 34 (7) years at ECRHS I), and 4,976 participants in the period ECRHS II-III (51.3% female, 42 (8) years at ECRHS II). Current smokers decreased during follow-up (30% in ECRHS I-II vs. 19% in ECRHS II-III). The relative number of participants with current asthma remained the same across the study waves. Overall, 9% of participants became obese from ECRHS-I to ECRHS-II and this proportion rose to 15% from ECRHS II to ECRHS-III. We observed that 37% of the study population was physically active at ECRHS-II which increased slightly to 42% at ECRHS-III.

- Table 1

The association between asthma and obesity is presented in **Supplementary Table E1** and **Figure 2**. Compared to 8.4% and 14.6% of non-asthmatics who developed obesity at ECRHS-II and ECRHS-III respectively, 10.7% and 16.9% asthmatics developed obesity at ECRHS-II and III. The absolute risk difference in asthmatics vs no asthmatics was 2.3% (95% CI 0.8 to 3.9%) and the relative risk (RR) was 1.21 (95%CI: 1.07 to 1.37). After adjusting for potential confounders (age, sex and smoking status at time  $t$ ), the association between asthma and the development of obesity remained significant (1.22; 1.07 to 1.38). The association was stronger among asthmatics without atopy (1.47; 1.17 to 1.86), asthmatics with longer disease duration (1.32; 1.10 to 1.59), asthmatics who used oral corticosteroids (1.99; 1.26 to 3.15) and those who used both oral and inhaled corticosteroids (2.07; 1.19 to 3.59).

- Figure 2

We conducted post hoc analyses to understand better the association between oral corticosteroids intake and incident obesity. The comparison between patients on continuous, short-course or use as rescue medication of OCS suggested a higher risk of obesity among those using continuously, but very small sample size precluded any kind of statistical testing (**Supplementary Table E2**).

The association of asthma and obesity was similar in males (1.27; 1.06 to 1.51) and females (1.20; 1.01 to 1.42, **Supplementary Table E3**). The association of asthma with new onset obesity was homogeneous across the participating countries (**Figure 3**) and centres (**Supplementary Figure E1**). The overall estimates from the meta-analyses were similar to that reported in the main analysis and there was no statistical evidence of heterogeneity ( $I^2=0$ , p-values for heterogeneity were 0.70 and 0.96 for country and centre, respectively).

- Figure 3

No evidence of physical activity as a mediator in the asthma-obesity association was observed (**Supplementary Table E4**). When stratified by smoking status, the risk of becoming obese in asthmatics was higher among current smokers (1.46, 1.12 to 1.90) and among never smokers (1.27, 1.08 to 1.49), while no association between asthma and obesity was observed among those who stopped smoking (0.95; 0.65 to 1.37) (**Supplementary Table E5**). In the sensitivity analyses, the estimates were comparable to the main analyses (**Supplementary Tables E6, E7, E8, E9 and E10**).

## **DISCUSSION**

In this prospective cohort study, we found that individuals with active asthma were at higher risk of developing obesity compared to individuals without asthma, that this association was higher among non-atopic asthmatics, those with long disease duration or those using oral corticosteroids, and that the association was not mediated by physical activity levels.

Our observation of accelerated weight gain among asthmatics is supported by a previous prospective study that demonstrated asthma to be associated with increased weight gain at a later stage in women,[21] although unlike our results, they did not find such association in men. Two recent longitudinal studies in children, one of them including more than 21,000 children from 16 European cohorts, showed that childhood asthma was a risk factor for obesity at a later age.[6, 7] Another recent report also demonstrated that children with high peak flow variability were on a steeper increase of BMI up to young adult life that was not associated with asthma.[8] This evidence suggests that asthma and obesity share several common physiological pathways and a bi-directional association between asthma and obesity is plausible.

It has been debated whether there is any association between atopy and increased body weight.[23] While several reports support this association, [24, 25] other studies have shown that the risk of being overweight is higher among the non-atopic than those with marked allergic sensitization.[26, 27] Our observation of a greater risk of obesity among non-atopic asthmatics indicates that allergic sensitization is unlikely to explain the association between asthma and obesity.

We observed that the risk of developing obesity was more pronounced among asthmatics who were on oral corticosteroids than those who were not, in agreement with previous reports, in adults and children with asthma, relating the intake of oral corticosteroids with abnormal weight gain.[28-31] Unfortunately we could not test the role of corticosteroids dose or duration due to small sample size of OCS users. The effects of long term use of oral corticosteroids on weight gain are well established in asthma and general population,[28, 32] and supported by several mechanisms, including but not limited to increased lipid uptake from the gut and storing in the peripheral tissues,[31] or increased insulin resistance.[33] However, we also found an increased and statistically significant risk of obesity among asthmatics who reported not having taken OCS. One could argue that, if asthma really causes weight gain, this effect would be higher among those with severe asthma, so the higher risk observed among OCS users is actually the result of

confounding by indication and not a result of the treatment itself.[34] This is supported by our findings of higher obesity risk among asthmatics of longer disease duration..

A potential explanation for asthma causing weight gain is through the reduction of physical activity levels. Patients with chronic respiratory diseases tend to be less physically active due to recurrent episodes of breathlessness or persistent wheezing.[35] However, our analyses do not support this hypothesis, as physical activity was not mediating the asthma-obesity association and this association remained after excluding those participants who did not perform physical activity due to breathlessness, in line with the previously mentioned study among asthmatic children who developed obesity on follow-up independent of physical activity.[6]

Another potential explanation would be via a role of smoking. Smoking cessation has been observed to augment weight gain at least in the short term.[36, 37] However, we found no association between asthma and incident obesity among participants quitting smoking. On the contrary, we observed greater relative risks among current smokers and non-smokers. Smoking has been observed to reduce the efficacy of steroid treatment in asthma [38-40], so it could be argued that asthmatics who smoke are at a higher risk of the effects of asthma (such as obesity) because of worse disease control. Altogether suggests that there may be mechanisms other than OCS use, reducing physical activity and smoking cessation, linking asthma to obesity, but these are yet unknown.

Our study outcomes are of significant clinical importance. First, our observation of higher obesity risk in asthmatics who took oral corticosteroids, advocates the minimal and precise use of oral corticosteroids in asthma.[44] Albeit current recommendations of oral corticosteroids for asthma management, several reports also indicate that oral steroids are still prescribed indiscriminately in asthma, sometimes, even without diagnosing the severity of the disease properly.[45-47] This could result in an increasing burden of adverse health effects in asthma, obesity being one of the major consequences. Secondly, the observation of a greater risk of obesity among non-atopic asthmatics directs our attention towards adult-onset asthma and supports increasing attention to the reduction of adult risk factors, such as occupational exposures that account for up to 25% of

adult-onset asthma.[48] Thirdly, we also observed a higher risk of obesity among asthmatics who were smokers. Although smoking cessation programmes have now become a part of the clinical management of respiratory and cardiovascular diseases, evidence shows that not all patients benefit from them, particularly in primary care.[49, 50] Advice on smoking cessation along with its plausible consequences (such as temporary weight gain) should also be discussed with the patients. Finally, although we did not find any evidence of physical activity mediating the asthma-obesity interaction, it must be noted that lifestyle factors also significantly influence weight gain. Thus, advice on healthy diet, proper physical activity and lifestyle modification should be warranted as part of asthma management.

The strengths of our study included its longitudinal design, allowing the exclusion of obese subjects at baseline, with a large cohort that was followed over a long period of time. Furthermore, we performed several sensitivity analyses to test the robustness of our results against assumptions about asthma or obesity miss-classification, residual confounding or model miss-specification. Lastly, the results were homogeneous across the participating countries which indicate that study findings can be extrapolated to other populations.

A limitation in this study is the potential bias in defining asthma and obesity status, given the lack of information on when events happened during the 10 years follow-up period. However, our results were robust to several sensitivity analyses. Although we were able to consider plausible known confounders, the effect of other lifestyle factors (such as diet, only available in a subsample of ECRHS at one single time point), psychosocial attributes, or genetic predisposition could not be analysed. Finally, we were limited to explore in detail the role of OCS on obesity risk because of the lack of detailed information on dosage, duration or their use for other diseases than asthma.

## **CONCLUSION**

In summary, we demonstrated that participants with asthma were at a higher risk of developing obesity later in life and the risk was more pronounced among those asthmatics who were non-atopic, those with asthma of longer duration and those on oral corticosteroids. These results support earlier results in children and warrant further clinico-epidemiological and experimental



research, in order to determine the mechanisms through which asthma could trigger obesity risk among adults.

## **AUTHOR CONTRIBUTIONS**

S Moitra, A-E Carsin, M Kogevinas, and J Garcia-Aymerich conceived the study design, analysed the results, interpreted the data, and drafted the manuscript. S Guerra interpreted the data; drafted the article or revised it; provided intellectual content of critical importance to the work described. All other authors revised the manuscript and provided critical comments. The joint first authors and the last author take the responsibility for the data integrity.

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## ***ECRHS II***

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### ***ECRHS III***

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## **CONFLICT OF INTEREST**

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## **DATA SHARING POLICY**

The datasets used and analysed during the current study are available from the authors upon reasonable request.

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**Table 1: Demographic profile of the study participants in ECRHS I-II and in ECRHS II-III**

	<b>ECRHS I-II n=7576</b>	<b>ECRHS II-III n=4976</b>
Sex (female), n (%)	3905 (51.5%)	2555 (51.3%)
Age <i>t</i> (years), mean (SD)	34.0 (7.1)	41.5 (7.8)
Age <i>t+1</i> (years), mean (SD)	42.7 (7.2)	53.9 (7.1)
Education, n (%)		
Low	813 (10.8%)	409 (8.5%)
Medium	2715 (36.0%)	1675 (34.7%)
High	4024 (53.3%)	2744 (56.8%)
Country, n (%)		
Australia	387 (5.1%)	212 (4.3%)
Belgium	528 (7.0%)	287 (5.8%)
Estonia	250 (3.3%)	132 (2.7%)
France	862 (11.4%)	737 (14.8%)
Germany	534 (7.0%)	545 (11.0%)
Iceland	434 (5.7%)	320 (6.4%)
Italy	512 (6.8%)	210 (4.2%)
Norway	500 (6.6%)	298 (6.0%)
Spain	1353 (17.9%)	806 (16.2%)
Sweden	1231 (16.2%)	749 (15.1%)
Switzerland	483 (6.4%)	403 (8.1%)
UK	502 (6.6%)	277 (5.6%)
Smoking status <i>t</i> , n (%)		
Never	3272 (43.3%)	2201 (44.4%)
Former	2043 (27.0%)	1814 (36.6%)
Current	2247 (29.7%)	939 (19.0%)
Current asthma <i>t</i> , n (%)		
No asthma	6859 (90.5%)	4495 (90.2%)
Current asthma, all	717 (9.5%)	490 (9.8%)
Current asthma, <i>without atopy</i>	271 (3.6%)	190 (3.8%)
Current asthma, <i>with atopy</i>	446 (5.9%)	300 (6.0%)
Current asthma, <i>≤20 years since onset</i>	406 (5.4%)	218 (4.4%)
Current asthma, <i>&gt;20 years since onset</i>	308 (4.1%)	266 (5.3%)
Current asthma, <i>no ICS</i>	494 (6.5%)	260 (5.2%)
Current asthma, <i>with ICS</i>	223 (2.9%)	230 (4.6%)
Current asthma, <i>no OCS</i>	664 (8.8%)	454 (9.1%)
Current asthma, <i>with OCS</i>	53 (0.7%)	36 (0.7%)
Current asthma, <i>only ICS</i>	183 (2.4%)	199 (4.0%)
Current asthma, <i>ICS &amp; OCS</i>	40 (0.5%)	31 (0.6%)
BMI <i>t</i> (kg/m <sup>2</sup> ), mean (SD)	23.3 (2.8)	24.1 (2.9)

BMI <i>t+1</i> (kg/m <sup>2</sup> ), mean (SD)	25.0 (3.6)	26.0 (3.8)
Obesity (yes) <i>t+1</i> , n (%)	655 (8.6%)	736 (14.8%)
Dyspnoea (yes) <i>t</i> , n (%)	256 (3.4%)	182 (3.7%)
Physical Activity (yes) <i>t+1</i> , n (%)	2627 (37.0%)	2029 (41.8%)

ECRHS: European Community Respiratory Health Survey; ICS: inhaled corticosteroids; OCS: oral corticosteroids;

BMI: body mass index.

Current asthma defined as a self-report of a doctor's asthma diagnosis and at least one of the following, within the last 12 months: waking up by an attack of shortness of breath, any asthma attack or use of asthma medications. Individuals with inactive asthma (reporting asthma diagnosis without any current symptoms) were excluded from the study (see Methods).

**Figure Legends:**

**Figure 1: Schematic representation of the study design**

**Figure 2: Association between asthma, asthma with atopy, asthma duration, and asthma with medication at  $t$  and incident obesity at  $t+1$ .** Data presented as relative risk (RR) and 95% confidence interval (95%CI). RR was calculated from modified Poisson regression with robust standard errors and subjects nested in centre as random effects. All models (for all participants) were adjusted for age, sex and smoking status at time  $t$ . See full figures in Supplementary Table E1.

**Figure 3: Meta-analysis results of the association between asthma at  $t$  and obesity at  $t+1$  by country**



Figure 1

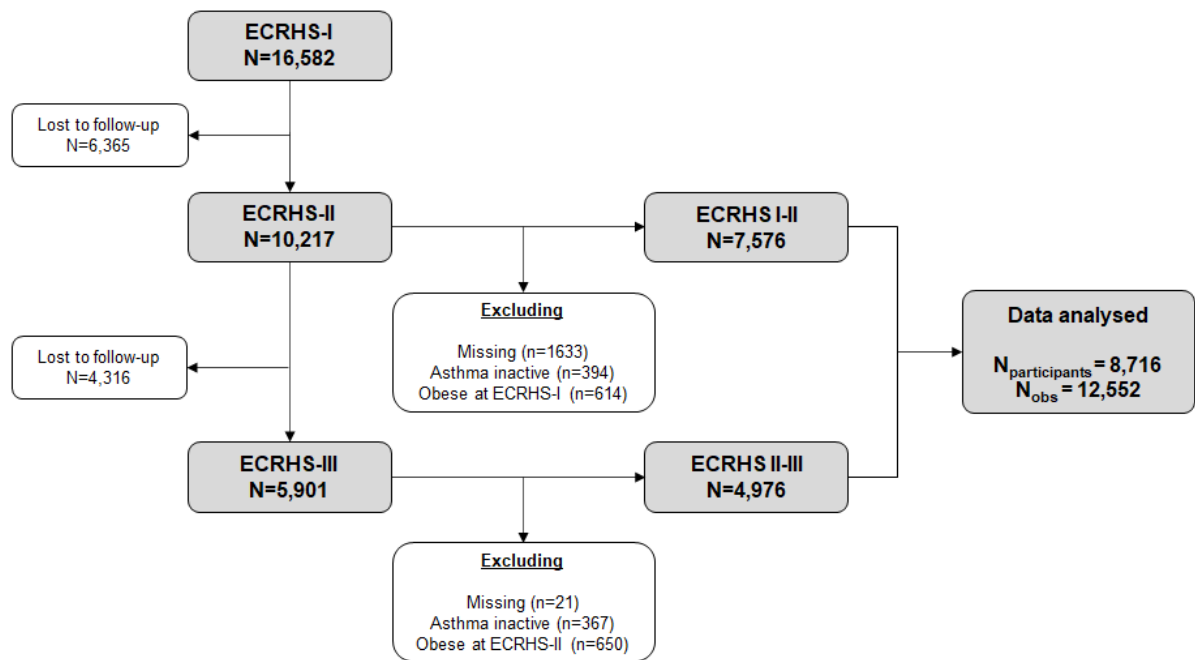
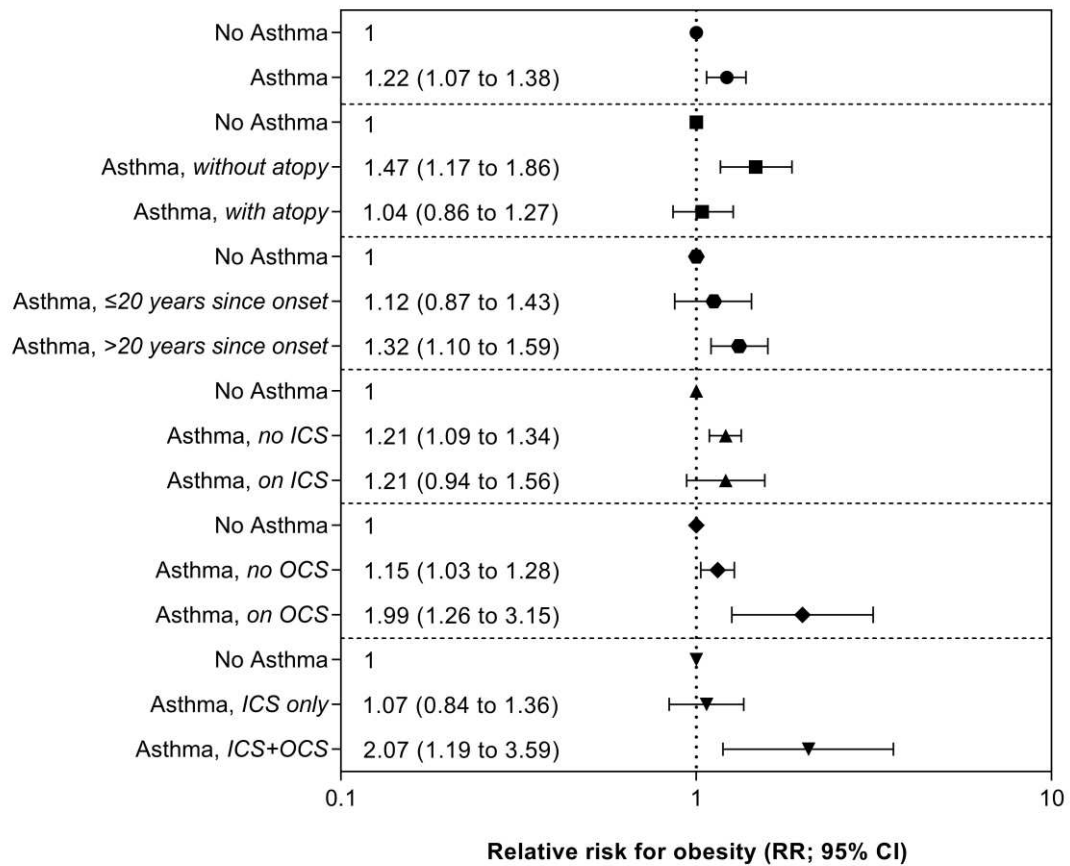


Figure 2



**Figure 3**

