Role of Leptin in the Association Between Body Adiposity and Persistent Asthma: A Longitudinal Study

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TITLE: Role of leptin in the association between body adiposity and persistent asthma: a longitudinal study

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The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS:

ZL, RN and RV designed and conducted the research; BL, NLM, CP, VS, RN and RV provided essential reagents or provided essential materials; ZL, OD, ODG, JG-A, MFC, VS, CAC, RN and RV analyzed data, performed experiments or statistical analysis; ZL, RN and RV wrote the manuscript and had primary responsibility for final content; all authors read, edited and approved the final manuscript.

Study Importance Questions

– What is already known about this subject?

- Obesity, or high body adiposity, has been associated with poor asthma control.
- Leptin, an adipocyte-derived pro-inflammatory protein, has been associated with asthma in both basic research and cross-sectional epidemiological studies. However, prospective data are limited in the literature.
- The role of leptin in the association between body adiposity and persistent asthma remained unclear due to methodological challenges of traditional analytic methods.

– What does your study add?

- This study provided prospective data regarding the associations between body adiposity, leptin, and persistent asthma.
- Using a causal analytic approach and including multiple measures of adiposity, we reported for the first time an indirect effect mediated by leptin in the association between adiposity and persistent asthma over time.

ABSTRACT

Objective: Obesity is a likely risk factor for asthma. However, underlying mechanisms by which obesity affects asthma activity remain poorly understood. We aimed to investigate the role of leptin, an adipocyte-derived pro-inflammatory protein, as a mediator in the association between body adiposity (assessed using body mass index (BMI), waist circumference (WC), and body fat percentage (BFP)) and persistent asthma.

Methods: A causal approach to mediation analysis was used to disentangle total and direct effects, and the indirect effect mediated by leptin, using data from the French prospective EGEA study (baseline: 2003–2007; follow-up: 2011–2013; mean follow-up time: 7 years). 331 participants with current asthma at baseline were included.

Results: Per 1-SD increment in BMI, WC and BFP, the adjusted odds ratios (ORs) of the total effect were 1.59 (95% CI: 0.95, 2.97), 2.06 (1.06–4.00), and 3.25 (1.01–9.41), respectively; the ORs of the indirect effect mediated by leptin were 1.68 (1.09, 2.46), 1.55 (0.99–2.57), and 1.99 (0.94–4.83), respectively.

Conclusions: Leptin partly (>60%) mediated the association between high body adiposity and persistent asthma over time. Using a newly developed analytic approach, this longitudinal study brought new insight into one mechanism by which obesity may affect asthma activity.

MAIN TEXT

Introduction

Obesity, or high body adiposity, has been associated with severity, poor control, and reduced response to standard therapy of asthma (1). Potential underlying mechanisms by which obesity affects asthma include genetic and nutritional factors, alterations in the gut microbiome, systemic inflammation, metabolic abnormalities and changes in lung anatomy and function (2). Among them, the role of the non-T_H2 components and in particular leptin, an adipocyte-derived pro-inflammatory protein, has raised great interest in the obesity–asthma activity association (3). Using cross-sectional data, a few studies have observed positive associations of serum leptin concentration with asthma severity, asthma control, or lung function in children, and to a lesser extent in adults (4–6). Nevertheless, whether leptin mediates the adiposity–asthma activity association remains unclear, partly due to limited prospective data and methodological challenges raised by traditional regression analyses, such as insufficient power for the tests of direct and total effects (7). A causal approach to mediation analyses (8), using longitudinal data, can help to address these issues.

When studying the role of biological markers on disease, prospective data are warranted to avoid reverse causation. Indeed, using a cross-sectional design does not allow concluding whether the modification in the concentration of the biological marker is a cause or a consequence of the disease status. Mediation analysis in the counterfactual framework (8) using longitudinal data can minimize such reverse causation and offers an appropriate approach to study the effect of leptin in the association between body adiposity and asthma activity.

When investigating the obesity–asthma activity association, most of the studies in the literature used BMI to measure body composition. However, BMI is a mixed measure of lean and fat mass, which may lead to potential misclassification of body adiposity. It has been recently proposed that other measures rather than only BMI are needed to understand the obesity–asthma association (9), such as body fat percentage measured through BIA and waist circumference (10). Investigating the association between these different measures of body composition and asthma activity may provide more insight into the obesity–asthma activity association.

In this context, we investigated the role of leptin as a potential mediator, using a causal approach to mediation analysis, in the association between three measures of adiposity (BMI, WC, and BFP) and change in asthma activity over time.

Methods

We used data from the French Epidemiological study on the Genetics and Environment of Asthma (EGEA, https://egeanet.vjf.inserm.fr/index.php/fr/) (11), with data from the second survey (EGEA2, 2003-2007) as baseline, and the third survey (EGEA3, 2011-2013) as follow-up. We only included adults with current asthma at EGEA2 (n=558). After excluding missing data on body adiposity (n=53 for BMI, n=59 for WC, and n=232 for BFP respectively) and leptin (n=77), participants lost to follow-up (n=65), and those with missing data on current asthma assessed at EGEA3 (n=32), 331 participants were included in the analyses using BMI, 325 in the analyses using WC, and 152 in the analyses using BFP.

Ever asthma was defined by being recruited as an asthma case in chest clinics at EGEA1 or responding positively to at least one of the two questions at EGEA1 or EGEA2: 1) "*Have you ever had attacks of breathlessness at rest with wheezing*?" and

2) "*Have you ever had asthma attacks*?". Among participants with ever asthma (n=715), current asthma was defined by having had during the past 12 months 1) asthma attacks, 2) asthma symptoms (wheezing, nocturnal chest tightness, attack of shortness of breath), or 3) medication use because of breathing problems. Persistent asthma was defined by having current asthma at both surveys (EGEA2 and EGEA3); remitted asthma was defined by having current asthma at EGEA2 only.

Measurements of body adiposity were performed by trained health technicians at EGEA2 according to standardized protocols (12). Using data obtained from BIA (800 μA, 50 kHz), BFP was computed according to the prediction equation proposed by Sun *et al.* (13).

Serum leptin concentration (ng/ml) was measured at EGEA2 using the Luminex xMAG® technique in a BioPlex system (Bio-Rad Laboratories, Inc. Berkeley, California, USA). An aliquot of the same serum pool was run by duplicate in each plate. In order to minimize inter-plate variability, values of leptin concentration were divided by the pool result of the same plate and expressed as ratios (14).

Age (continuous), sex, smoking status (never, ever), educational level (university or equivalent or not), physical activity (metabolic equivalents per week as previously defined (15)), and total energy intake (continuous), assessed at EGEA2, were considered as potential confounders because they have been reported to be associated with both body adiposity and asthma activity in the literature. In our study, as expected, participants with a greater body adiposity were more often classified as persistent asthma (Table 1), and they were older, more often men, never smokers, with a low educational level, not physically active, and with a high energy intake, as compared to participants with lower body adiposity (15).

To disentangle the direct effect of adiposity on persistent asthma from the indirect effect mediated by leptin, we applied a mediation model in the counterfactual framework as previously described (8) (**Figure 1**). When relevant, the proportion of the adiposity effect explained by leptin in the relationship between adiposity and persistent asthma was calculated as $(OR_{TE}–OR_{DE}) / (OR_{TE}–1)$, where OR_{TE} and OR_{DE} were respectively the odds ratio of total and direct effects (16).

Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris). All participants provided written informed consent.

Results

Main characteristics are presented in **Table 1**. The mean follow-up time was 7 years. Participants with persistent asthma and those with remitted asthma were similar regarding age (*P*=0.12), sex (*P*=0.44), educational level (*P*=0.99), total energy intake (*P*=0.67), physical activity (*P*=0.83), and smoking status (*P*=0.18). However, compared with participants with remitted asthma, participants with persistent asthma (n=305; 92%) had higher BMI (24.3 *vs*. 22.6 kg/m^2, *P*=0.05), greater waist circumference (83 *vs*. 77 cm, *P*=0.03), higher BFP (25.0% *vs*. 21.5%, *P*=0.06), and higher concentration of leptin (4.4 *vs*. 3.0 ng/ml, *P*=0.03). WC correlated strongly with BMI in men and in women (both r>0.8). BFP correlated more strongly with BMI in women (r=0.89) than in men (r=0.74).

For BMI, we observed a positive borderline significant total effect on persistent asthma over 7 years, with a significant positive indirect effect mediated by leptin (**Figure 2**) and a negative direct effect. The latter precludes the calculation of the

proportion of the association mediated by leptin (16). For WC and BFP, we observed similarly a significant positive total effect on persistent asthma, with a borderline significant positive indirect effect; the indirect effect mediated through leptin accounted for 64% and 63% of the total effect respectively for WC and for BFP.

Discussion

Applying a causal approach to mediation analysis, we reported for the first time an indirect effect mediated by leptin in the association between adiposity and persistent asthma over time. Nevertheless, due to the limited sample size and borderline significant findings, and to the many other inflammatory biomarkers that are potentially involved in asthma, the results need to be interpreted with caution.

A recent study using the traditional approach to mediation analysis concluded that leptin mediated the association between BFP and asthma control assessed by Asthma Control Questionnaire (17). However, this study was mainly limited by the lack of causality in study design (i.e. cross-sectional) and in analytic approach. Animal studies support the biological plausibility of the hypothesis that adiposity may affect asthma activity through increased leptin level. Leptin administration to wild-type mice resulted in increased airway inflammation (18). Indeed, leptin enhances phagocytosis, activation, proliferation, and alternation of macrophages, and induces production of pro-inflammatory cytokines, including tumour-necrosis factor (TNF) α, interleukin-6 (IL-6), and reactive oxygen species (ROS) (19), which are likely involved in pathophysiological processes of asthma. Taken together, we believe that leptin is a likely mediator in the association between body adiposity and persistent asthma activity.

Other non-T_H2 components may also be involved in the association between body adiposity and persistent asthma activity. Low concentration of serum adiponectin, which is an anti-inflammatory biological marker mainly secreted by adipocytes (20), is associated with higher asthma incidence in women according to a prospective study (21). In addition, given the complex effect of insulin in the metabolism and inflammation process (22,23), the role of insulin in the association between obesity and asthma activity merits further investigation. Besides, as leptin and adiponectin can regulate the production of pro-inflammatory cytokines (e.g. IL-6 and TNF-α) by macrophages, such cytokines may also lie in the causal pathway of the association between body adiposity and persistent asthma activity (18). Beyond adipocyte-derived pro-inflammatory protein, many other inflammatory biomarkers play a key role in asthma, including matrix metalloproteinase (MMP), chemokines and their receptors (CCR), more recently LIGHT and its receptor, and thymic stromal lymphopoeitin (TSLP) (23). Interestingly, in obese patients, the gene expression and/or concentrations of interleukin (IL)-4, ADAM-33, LIGHT, MMP-9, and CCR-2 are reduced following gastric bypass surgery and weight loss (22). Further studies, with a larger study sample, using a model including multiple pro-inflammatory factors as well as the interrelations between these factors would be helpful to understand the association between body adiposity and asthma activity. A better understanding of the underlying mechanisms by which obesity affects asthma is the first step toward the development of effective treatment to address this unmet medical need.

Compared with BMI, for which the sample size was the largest among the three measures of adiposity, we reported stronger total effects for WC and BFP on persistent asthma. This finding may be partly explained by the inaccurate measure of

body adiposity using BMI (i.e. mixed measure of both lean and fat mass), particularly in men.

Using longitudinal data, this study adds further evidence on the role of leptin in the adiposity-asthma activity association and introduced an interesting analytic approach. However, because of the relatively small sample size, it was not possible to study the subgroup effects; the mechanisms underlying the adiposity–asthma activity association might be different according to sex, age of asthma-onset, and allergic sensitization.

Conclusion

In conclusion, leptin is likely to have partly mediated the association between adiposity and persistent asthma over time. Further larger prospective studies, using causal analytic approaches and including multiple measures of adiposity, are likely to provide new insight into the mechanisms by which obesity affects asthma activity.

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FIGURE LEGEND:

Figure 1 Direct acyclic graph of the proposed mediation model. DE: direct effect; IDE: Indirect effect; TE: Total effect.

Figure 2 Association between measures of body adiposity and persistent asthma, taking into account leptin as a mediator. OR (95%CI) were estimated for each increment of 1 SD in BMI (4.3 kg/m^2), waist circumference (13.8 cm), and body fat percentage (7.9 %). DE: direct effect; IDE: Indirect effect; TE: Total effect.