

Lower body mass index is associated with a higher risk of giant cell arteritis: a systematic review and meta-analysis

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Objective: To characterize the possible association between body mass index (BMI) and risk of giant cell arteritis (GCA).

Methods: We conducted a systematic review of observational studies (case-control or cohort study) that (I) reported BMI of patients with GCA prior to the diagnosis of GCA compared with subjects without GCA and (II) provided relative risk (RR), odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI) from its regression analysis. Meta-analysis of the included studies was then performed to estimate the pooled effect using generic variance method of DerSimonian and Laird.

Results: Three studies encompassing 141 patients with GCA and 85,736 controls met our eligibility criteria and were included in the data analyses. We demonstrated a statistically significant inverse relationship between BMI and risk of subsequent development of GCA as the risk increased by 8% when BMI was reduced by 1.0 kg/m² (pooled OR of 0.92/kg/m²; 95% CI, 0.88-0.96).

Conclusions: Our study demonstrated a statistically significant inverse relationship between BMI and risk of subsequent development GCA. The pathophysiologic link behind this negative correlation is not well-characterized and further investigation is required.

Keywords: Giant cell arteritis (GCA); systematic review; epidemiology; meta-analysis; body mass index (BMI)

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Introduction

Giant cell arteritis (GCA) is a form of vasculitis characterized by granulomatous inflammation of medium and large-sized arteries (1). It is the most common vasculitis in Western countries with the highest reported incidence in Scandinavian countries and Minnesota, United States of America. In these populations, with a shared ethnic background, an annual incidence of ~20/100,000 population >50 years of age has been estimated (2,3). GCA typically affects women older than 50 years of age with a peak incidence among those aged 75-85 years (4,5). Patients with

GCA usually present with characteristic signs and symptoms of systemic inflammation and cranial ischemia including new-onset headache, visual changes, jaw claudication and scalp tenderness (1,4). GCA is associated with significant morbidity and mortality, including visual loss from ischemic optic neuropathy, cerebrovascular accident, aortic aneurysm and aortic dissection, secondary to the damaged arterial wall and its ischemic complications (1,5).

There are limited data on predictors of GCA. In 2006, Larsson had demonstrated a statistically significant inverse relationship between risk of developing GCA and body

mass index (BMI) (6). This raises the question of whether the higher BMI could be a protective factor against GCA. Nevertheless, subsequent epidemiological studies attempting to answer this question yielded inconsistent results (7,8). Thus, to further investigate this possible association, we conducted a systematic review and meta-analysis of epidemiological studies that investigated the relationship between BMI and risk of subsequent development of GCA.

Methods

Search strategy

A comprehensive search was conducted by two investigators (P.U. and C.T.) who independently searched published studies indexed in MEDLINE and EMBASE database from inception to November 2014 using the search terms described in Supplementary data. References of selected articles were also manually searched.

Inclusion criteria

The inclusion criteria were as follows: (I) observational study (case-control or cohort study) published as original study or conference abstract reporting BMI of patients with GCA prior to the diagnosis of GCA compared with subjects without GCA (II) relative risk (RR), odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI) from regression analysis were provided.

Study eligibility was independently determined by each investigator noted above. Any disagreements were resolved by with the senior investigator (K.J.W.). Quality of the included cohort and case-control studies was, again, independently evaluated by the two investigators using the Newcastle-Ottawa quality assessment scale (9) which assessed each study with eight items in three areas including (I) the selection of the study groups, (II) the comparability of cases and controls, and (III) the ascertainment of the exposure or the assessment of outcome of interest for case-control or cohort studies respectively.

Exclusion criteria

The exclusion criteria were as follows: (I) interventional study; (II) descriptive study without control group; (III) cross-sectional study as this type of study cannot evaluate the temporal relationship between BMI and risk of GCA.

Data extraction

All investigators independently extracted data from each study using a standardized data collection form. This information was extracted: last name of the first author, title of the study, study design, year of publication, country where the study was conducted, numbers of cases and controls, method used to identify cases and controls, criteria used for the diagnosis of GCA, method used to measure BMI, time when BMI was measured and basic epidemiological data of cases and controls. Any discrepancies in data extraction were resolved by referring back to the original studies.

Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird (10). HRs and RRs were used as an estimate for OR. Fixed effect model was utilized. Cochran's Q test was used to determine the statistical heterogeneity of this study. This test was complemented with the I^2 statistic, which quantified the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0% to 25% indicates insignificant heterogeneity, 26% to 50% indicates low heterogeneity, 51% to 75% indicates moderate heterogeneity, and 76% to 100% indicate high heterogeneity (11).

Results

Our search strategy yielded 268 potentially relevant studies (63 articles from Medline and 205 articles from EMBASE). After the exclusion of 53 duplications, 215 articles underwent title and abstract review. Two hundred and ten articles were excluded as they were clearly not observational studies, were not conducted in patients with GCA or did not report patient's BMI, leaving 5 articles for full-length article review. Two articles were excluded since they evaluated the association between BMI and risk of subsequent development of polymyalgia rheumatica, but not GCA (12,13). Three studies [(two case-control studies (6,7) and one cohort study (8)] with 141 patients with GCA and 85,736 controls met our eligibility criteria were

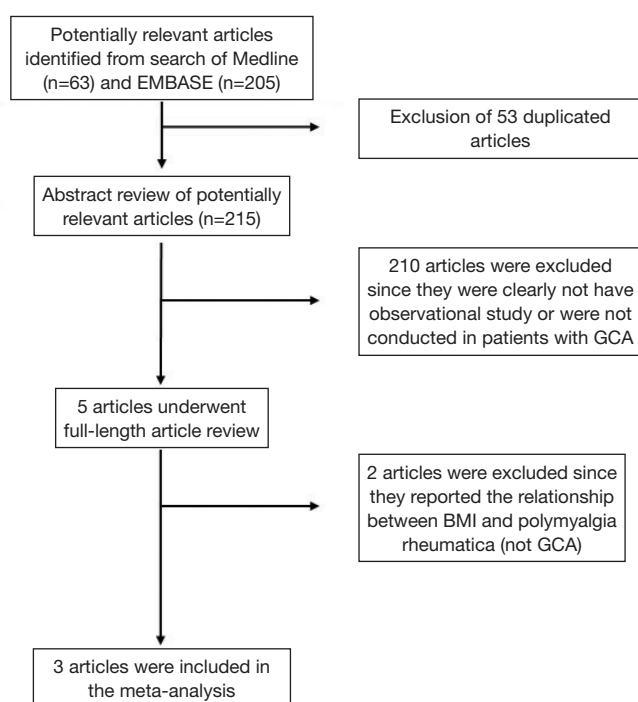


Figure 1 Outline of our search methodology. GCA, giant cell arteritis.

included in our data analyses. *Figure 1* outlines the search methodology and review process. The detailed characteristics of the included studies are illustrated in *Table 1*.

Our study is the first meta-analysis to demonstrate a statistically significant inverse relationship between BMI and risk of subsequent development of GCA as the risk increased by 8% when BMI was reduced by 1.0 kg/m² (pooled OR of 0.92/kg/m²; 95% CI, 0.88-0.96). The statistical heterogeneity was moderate with an *I*² of 70%. *Figure 2* demonstrates the forest plots of this meta-analysis.

As the statistical heterogeneity was not low in this meta-analysis, we also performed another analysis using random-effect model which yielded a slightly different pooled estimated effect and a wider 95% CI (pooled OR of 0.94/kg/m²; 95% CI, 0.86-1.03).

As the study by Larsson *et al.* (6) and Harpsøe *et al.* (8) included only female subjects while study by Jakobsson *et al.* (7) was the only that also included male subjects, we performed a sensitivity analysis by using the data of female subjects (instead of all subjects) from Jakobsson's study for the data analysis. This sensitivity analysis did not significantly alter the results as the pooled OR only slightly decreased to 0.91/kg/m² with 95% CI of 0.87-0.96.

Evaluation for publication bias

We did not conduct an evaluation for publication bias as only three studies were included in this meta-analysis.

Discussion

A negative correlation between BMI and risk of GCA was demonstrated in this meta-analysis. Risk of subsequent development of GCA was reduced by 8% with every 1 kg/m² increase in BMI. It is unclear as to why individuals with higher BMI have a lower risk of GCA. There are few potential explanations.

The first hypothesis is related to the relationship between BMI and diabetes mellitus (DM). GCA is an antigen-driven inflammatory process, although the inciting antigen(s) have yet to be identified (14). These inciting antigen(s) are recognized by dendritic cells residing in the arterial wall, which then initiate the inflammatory cascade by recruiting T cells and macrophages to form granulomas (15-17). Patients with DM may have a lower likelihood of developing GCA as a result of the decreased responsiveness of dendritic cells and T cells to the putative antigen(s) secondary to hyperglycemic state (18-21). In fact, several epidemiological studies have demonstrated a lower prevalence of DM in patients with GCA compared with sex and age-matched controls (22-27). It is well documented that individuals with higher BMI have a higher risk of the development of DM (28-30) and this could be responsible for their lower risk of GCA.

The second possible hypothesis is related to the anti-inflammatory property of female sex hormones (31-33) as estrone, the principal estrogen in male and postmenopausal female, is formed primarily by the conversion of adrenal androstenedione in adipose tissue (34). Moreover, estrogen has been shown to augment the responsiveness of hypothalamo-pituitary-adrenal axis to inflammatory stimuli (35,36). Higher endogenous estrone production in individuals with a higher BMI, which implies a higher amount of total body adipose tissue, could have anti-inflammatory effects and, thus, prevent autoimmune disorders such as GCA.

The major strength of this meta-analysis is the quality of the included studies and the ability to demonstrate the temporal relationship between BMI and GCA as all three studies measured their cohort's BMI before the onset of GCA. Nonetheless, there are several limitations and, thus, our results should be interpreted with caution.

First, all of the included studies used medical registry-based database to identify GCA cases, raising a concern of

Table 1 Main characteristics of the included studies in the meta-analysis

Variables	Larsson <i>et al.</i> (6)	Jakobsson <i>et al.</i> (7)	Harpsoe <i>et al.</i> (8)
Country	Sweden (Goteborg region)	Sweden (Malmo region)	Denmark
Study design	Case-control	Case-control	Prospective cohort
Year	2006	2014	2014
Cases	Cases were identified by using database of the department of pathology, Sahlgrenska University Hospital. All cases of positive TAB in 1991-2000 were reviewed	Cases were identified by using database of Malmo University hospital and National Hospital Discharge. Cases were then linked to the database of Malmo Diet Cancer Study and Malmo Preventive Medicine Program, two community-based health surveys performed in Malmo Sweden, that were conducted in 1991-1996 and 1974-1992, respectively. Subjects with the diagnosis of GCA before participation in these surveys were excluded	Cohort of 75,008 women were originally enrolled in the Danish National Birth Cohort in 1996-2002. Recruitment by general practitioners took place in early pregnancy throughout Denmark. This cohort was longitudinally followed until December 2011. Incident cases of GCA from this cohort were identified by using Danish National Patient Register which covered all inpatient and outpatient contact
Diagnosis of GCA	Positive TAB plus clinical diagnosis of GCA from medical record review	Diagnostic code from the database plus medical record review. Cases needed to fulfill the 1990 ACR criteria for GCA	Diagnostic code from the database
Control	Women aged 49 to 69 years who had participated in routine mammogram screening in the Swedish national program for the prevention of breast cancer	Sex and age-matched, randomly selected from the same database. Control had to be alive and free of GCA when the index case was diagnosed with GCA	Subjects in the cohort who did not have GCA
Method of BMI measurement	Questionnaires were sent to both groups asking for their weight and height at menopause	Questionnaires were used to ask for weight and height during the surveys	Structured interview at enrollment
Timing of BMI measurement	At menopause	At the time the surveys were conducted	Before pregnancy
Mean age at diagnosis of cases and controls (years)	64.1/NA	71.0/71.0	NA/NA
Percentage of female in cases and controls	100.0/100.0	70.0/70.0	100.0/100.0
No. of cases	49	83	9
No. of control	10,405	332	74,999
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 stars; comparability: 1 star; outcome: 2 star	Selection: 4 stars; comparability: 2 stars; outcome: 2 stars	Selection: 3 stars; comparability: 2 stars; outcome: 2 stars

GCA, giant cell arteritis; NA, not available; BMI, body mass index; TAB, temporal artery biopsy.

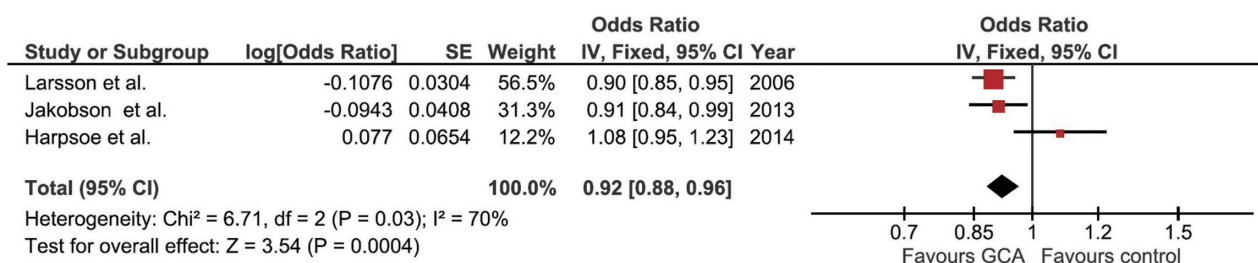


Figure 2 Forest plot of all included studies.

coding inaccuracy and incompleteness. Second, statistical heterogeneity was present in this study. Third, two out of three studies exclusively recruited only female patients. This might jeopardize the generalizability of our results, particularly for male patients. Fourth, we cannot perform the evaluation for publication bias and, thus, publication bias might be present. Fifth, there was a big difference between the numbers of cases and controls which might affect the validity of the comparison. Moreover, this is a meta-analysis of observational studies which, at the best, can only demonstrate an association, not causality. Therefore, we cannot make a conclusion that BMI itself versus other potential confounders reduce the GCA risk. For example, smoking is associated with a lower BMI (37,38) and has also been shown to be a strong risk factor for GCA (39,40).

Conclusions

In conclusion, our meta-analysis demonstrated a statistically significant inverse relationship between BMI and risk of subsequent development GCA. The risk increased by 8% when BMI was reduced by 1.0 kg/m^2 . Our findings should be considered hypothesis-generating and further research is required.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary data

Search strategy: Ovid Medline

- (I) exp Polymyalgia Rheumatica/
- (II) polymyalgia rheumatica.mp.
- (III) exp Giant Cell Arteritis/
- (IV) giant cell arteritis.mp.
- (V) temporal arteritis.mp.
- (VI) temporal arterit\$.mp.
- (VII) cranial arterit\$.mp.
- (VIII) horton disease\$.mp.
- (IX) pmr.mp.
- (X) or/1-9
- (XI) Cohort Studies/
- (XII) comparative study/
- (XIII) follow-up studies/
- (XIV) prospective studies/
- (XV) risk factors/
- (XVI) cohort.mp.
- (XVII) groups.mp.
- (XVIII) multivariate.mp.
- (XIX) compared.mp.
- (XX) or/11-19
- (XXI) body mass index.mp. or exp Body Mass Index/
- (XXII) body weight.mp. or exp Body Weight/
- (XXIII) obesity.mp. or exp Obesity/
- (XXIV) or/21-23
- (XXV) 10 and 20 and 24

Search strategy: EMBASE

- (I) body mass index.mp. or exp body mass/
- (II) body weight.mp. or exp body weight/
- (III) obesity.mp. or exp obesity/
- (IV) or/1-3
- (V) clinical article/
- (VI) controlled study/
- (VII) major clinical study/
- (VIII) prospective study.mp. or exp prospective study/
- (IX) cohort.mp.
- (X) compared.mp.
- (XI) groups.mp.
- (XII) multivariate.mp.
- (XIII) or/5-12
- (XIV) polymyalgia rheumatica.mp. or exp rheumatic polymyalgia/
- (XV) giant cell arteritis.mp. or exp giant cell arteritis/
- (XVI) temporal arteritis.mp. or exp temporal arteritis/
- (XVII) cranial arterit\$.mp.
- (XVIII) horton disease\$.mp.
- (XIX) pmr.mp.
- (XX) or/14-19
- (XXI) 4 and 13 and 20