



## Increased asthma and adipose tissue inflammatory gene expression with obesity and Inuit migration to a western country



Vibeke Backer <sup>a,\*</sup>, Katherine J. Baines <sup>b,c</sup>, Heather Powell <sup>b,c</sup>, Celeste Porsbjerg <sup>a</sup>, Peter G. Gibson <sup>b,c</sup>

<sup>a</sup> Department of Respiratory Medicine L, Bispebjerg Hospital, Copenhagen University Hospital, Copenhagen, Denmark

<sup>b</sup> Priority Research Centre for Asthma and Respiratory Diseases, Hunter Medical Research Institute, The University of Newcastle, New Lambton Heights, NSW 2305 Australia

<sup>c</sup> Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton, NSW 2305 Australia

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### ABSTRACT

**Background:** An overlap between obesity and asthma exists, and inflammatory cells in adipose tissue could drive the development of asthma. Comparison of adipose tissue gene expression among Inuit living in Greenland to those in Denmark provides an opportunity to assess how changes in adipose tissue inflammation can be modified by migration and diet.

**Objective:** To examine mast cell and inflammatory markers in adipose tissue and the association with asthma.

**Methods:** Two Inuit populations were recruited, one living in Greenland and another in Denmark. All underwent adipose subcutaneous biopsy, followed by clinical assessment of asthma, and measurement of AHR. Adipose tissue biopsies were homogenised, RNA extracted, and PCR was performed to determine the relative gene expression of mast cell (tryptase, chymase, CPA3) and inflammatory markers (IL-6, IL-1 $\beta$ , and CD163).

**Results:** Of the 1059 Greenlandic Inuit participants, 556 were living in Greenland and 6.4% had asthma. Asthma was increased in Denmark (9%) compared to Greenland (3.6%,  $p < 0.0001$ ) and associated with increased adipose tissue IL-6 gene expression and increased BMI. There was no association between asthma and adipose tissue mast cell gene expression. Pro-inflammatory gene expression (IL-6, IL-1 $\beta$ ) was higher in those living in Denmark, and with increasing BMI and dietary changes. The anti-inflammatory (M2) macrophage marker, CD163, was higher in Greenland-dwelling Inuit ( $p < 0.01$ ).

**Conclusions:** No association was found between gene expression of mast cell markers in adipose tissue and asthma. Among Greenlandic Inuit, adipose tissue inflammation is also increased in those who migrate to Denmark, possibly as a result of dietary changes.

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## 1. Introduction

The prevalence of asthma and obesity is increasing worldwide, and recent studies have shown that weight gain can precede the development of asthma in western societies [1,2]. Asthma and obesity are both chronic inflammatory diseases and mounting evidence suggests that the obesity-related asthma phenotype may involve different mechanisms to the classical T<sub>H</sub>2-dependent-

eosinophilic inflammatory process [3–6]. Both asthma and obesity can be associated with chronic low-grade systemic inflammation involving acute phase proteins such as C-reactive protein and pro-inflammatory cytokines such as IL-6 and IL-1 $\beta$ , which may be driven by adipose tissue inflammation [7]. Macrophages with a pro-inflammatory phenotype, termed M1, produce inflammatory cytokines such as IL-6 and IL-1 $\beta$ , whereas those with an anti-inflammatory (M2) phenotype are CD163 positive [5]. Caloric excess, that is typical of a western diet, has been shown in animal models to induce both systemic inflammation and adipose tissue inflammation, involving an increase in the number of M1 macrophages in the stromal vascular fraction of adipose tissue. In

\* Corresponding author. Dept of Respiratory Medicine L, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark.

E-mail address: [backer@dadlnet.dk](mailto:backer@dadlnet.dk) (V. Backer).

contrast, consumption of n3 fatty acids that is typical of an Arctic diet [8–11] can reduce these effects [12,13]. In addition, mast cells, which have a well-established role in asthma, have now been identified as potentially relevant in the pathogenesis of obesity where adipose tissue mast cells are increased and are a potential source of adipocytokines [14–16].

The Inuit population of Greenland are a genetically homogenous population with wide variations in diet and lifestyle. The Inuit population living in Greenland has a diet high in fish and arctic marine mammals which are rich in polyunsaturated (n-3) fatty acids [9]. Greenland Inuit frequently migrate from Greenland to Denmark, where they experience significant dietary changes, including increased consumption of a Western diet and increasing obesity [17]. We have reported that Greenland Inuit living in Denmark have a markedly higher prevalence of asthma when compared to Inuit living in Greenland. We have also identified that both low-grade systemic inflammation [18] and dietary intake adversely [19] impact lung function in this population. We therefore sought to characterise the relationship between adipose tissue inflammation and asthma in these populations. Our hypothesis was that the presence of mast cells and macrophages in adipose tissue could lead to adipose tissue inflammation, which might be associated with asthma symptoms or AHR. We collected adipose tissue, responses to a questionnaire on asthma as well as clinical measurements of airway diseases in a population sample and examined the association between inflammatory markers in adipose tissue in individuals with and without asthma.

## 2. Methods

### 2.1. Study design

Adult Greenlanders were recruited and assessed between 1997 and 2001 [20]. A random sample of first generation Inuit immigrants living in urban areas of Denmark was accessed by the civil registration list consisting of 3513 Greenlanders above 18 years living in Denmark on a permanently basis with the similar age distribution as found among Greenlanders in Greenland. A random sample of Inuit from the main city of Greenland (Nuuk) excluding all Danes living in Nuuk as well as the entire population from an isolated area of four small settlements on the northwest coast (Uummannaq) were accessed via the Greenland population register [21]. The overall participation rate was 58.6% among the males Inuits, and 71.7% among the female Inuits leaving an overall participation rate of 65.3% [20].

In total, 1428 Inuits had a questionnaire based interview performed concerning respiratory symptoms, diet, education, and smoking, 1227 then proceeded to clinical examination and subcutaneous gluteal adipose tissue biopsy. 168 were excluded because of insufficient RNA in the biopsy ( $n = 154$ ) or insufficient clinical data ( $n = 14$ ).

Of the 1059 participants who were included in the present analysis, 503 subjects were residing in Denmark, and 556 in Greenland; 353 subjects from the main city in Greenland (Nuuk) and 203 subjects from 4 small settlements (Uummannaq) (Table 1). Ethnicity was confirmed based upon ancestry of the subject's grandparents.

This study was approved by the Local Ethics Committee of Copenhagen, Denmark and the Ethics Committee of Greenland. This approval was registered with The University of Newcastle's Research Ethics Committee (H-2013-0408). All participants received both oral and written information, and had given their informed written consent before enrolment.

### 2.2. Area of examination

Greenland is an island at the Arctic Circle with a population of 55,000.

**Nuuk**, the main city of Greenland, is located 250 km south of the Arctic Circle with a population of 13,500. Nuuk has elements of a westernized lifestyle, in terms of housing, food and jobs, but with accessibility to more traditional living. Airplanes and larger ships can reach Nuuk all year around. The Gulf Stream reaches this part of Greenland, preventing the sea from freezing during winter. The climate is arctic with a mean annual temperature of  $-1.9\text{ }^{\circ}\text{C}$  ( $+6.5\text{ }^{\circ}\text{C}$  in July).

**Uummannaq**, a small rural town and settlements of Greenland, is located 500 km north of the Arctic Circle. The town is reachable by helicopter and 6 rural remote settlements (villages) are reachable by boat only during summer (July/August). Their inhabitants live mainly as hunters and fishermen, and are isolated during winter from September to June. The climate is arctic with a mean annual temperature of  $-7.4\text{ }^{\circ}\text{C}$  ( $+4.0\text{ }^{\circ}\text{C}$  in July).

**Denmark** is a European country of 5.5 million inhabitants, with a westernised lifestyle including indoor pets, office workers, fast food and tobacco consumption. The climate is temperate with an annual mean temperature of  $+8.0\text{ }^{\circ}\text{C}$  ( $+16.5\text{ }^{\circ}\text{C}$  in July).

### 2.3. Questionnaire data collection

The questionnaires used in the present survey were primarily developed in Danish, then translated into Greenlandic, and re-translated back to into Danish. Data regarding age, gender, diet, place of residence, socioeconomic status, occupation, and tobacco smoking status were collected. Current smoking was defined as reported daily tobacco consumption during the last year. Ex-smoking was defined as cessation of smoking more than 6 months previously. Dietary assessment involved a 3-month recall by interview carried out with specifications of certain traditional Greenlandic food items, including whale, seal, fish, wild meat, vegetables and fruit. The food frequency questionnaire has been used in several surveys in Greenland [22–24] and was validated with biomarkers [25].

### 2.4. Definition of disease outcomes

Asthma was defined as, doctors diagnose of asthma or asthma like symptoms such as attacks of shortness of breath, wheezy, cough, exercise-induced asthma symptoms as well as respiratory symptoms at night. These symptoms should also happen outside periods of infections and could be induced by factors such as allergens, fumes, dust, and other risk factors. Current asthma as asthma within the last 12 months, chronic mucous hypersecretion was cough and mucous for at least 3 month in a row, for at least 2 years, and lastly COPD were defined as mucous hypersecretion and signs airway obstruction  $\text{FEV}_1/\text{FVC} < 70\%$  [21].

### 2.5. Clinical examination

Height (cm) was measured without shoes using a stadiometer, and weight (kg) was measured while wearing light clothes. Lung function was measured using maximum expiratory flow volume according to the standards specified by the ERS and ATS [26], using a Vitalograph Spirometer (Spiropharma®, Copenhagen, Denmark). All participants had a methacholine provocation performed using the Cockcroft methods [27], after which a dose response ratio (DRR) was calculated [28]. Subcutaneous gluteal adipose tissue was

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