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Fat Distribution and Arterial Stiffness

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General Introduction

INTRODUCTION

Excessive body fat and, in particular, a central pattern of fat distribution, is an independent predictor of cardiovascular risk [1-3]. Furthermore, it has been demonstrated that individuals with obesity are likely to have an increase in arterial stiffness [4], which is an independent predictor of cardiovascular disease [5,6]. Obesity-related increases in arterial stiffness have been proposed as one of the potential pathways through which (central) obesity could lead to cardiovascular disease (CVD) [4,7].

Arterial stiffness, what is it?

The arteries have two important functions. The first one is to act as a *conduit* from heart to arterioles, in order to deliver blood to tissues and organs according to their needs. The second function is to act as a *cushion*. By smoothing pressure fluctuations, flow variability imposed by the intermittent contracting heart is reduced, so that the blood is directed to organs and tissues in an almost steady stream [8].

Structurally, the arterial tree can be divided in two compartments: a (proximal) elastic and a (distal) muscular part. Although all arteries of the vascular tree participate in the two aforementioned functions, proximal arteries (i.e. the aorta and its main branches) have a dominant role in cushioning, whereas distal muscular arteries also contribute to flow regulation. Due to their anatomical structure, the proximal compartment is characterized by optimal elasticity/compliance, whereas the distal compartment is characterized by higher stiffness [9]. In accordance, ageing, drugs and risk factors have differential effects along the arterial tree [10-12]. Arterial stiffening impairs the ability of the arterial system to handle the pressure wave that occurs during cardiac election. Stiffening of the arterial tree leads to increased systolic blood pressure, decreased diastolic blood pressure, increased left ventricular mass, and decreased diastolic perfusion [13,14]. The principal clinical complications of arterial stiffness, such as myocardial infarction, stroke and heart failure, usually occur in middle-aged or older people. However, arterial stiffening already starts in childhood [15].

Body fatness and body composition, how do they contribute to CVD?

Central (or abdominal) fat can be distinguished into subcutaneous abdominal fat and intra-abdominal fat. It has been postulated that especially intra-abdominal fat (also referred to as 'visceral fat') is detrimental because it directly releases free fatty acids into the portal vein, causing reduced hepatic insulin sensitivity, increased gluconeogenesis and dyslipidemia [16,17]. In contrast, peripheral fat (i.e. limbs) has been suggested to have a protective effect through uptake and storage of free fatty acids [18].

The secretory functions of adipose tissue are probably also subject to regional variations [19,20]. Abdominal fat and peripheral fat may differ in secretion of adipose derived proteins that influence the metabolism, vascular function, vascular structure and this way arterial stiffness. The pathobiological mechanisms explaining why especially central body fatness is associated with arterial stiffness remains largely unknown, however. One mechanism may be an altered profile of adipokine secretion, such as hyperleptinaemia [21-24] and/or hypoadiponectinaemia [25-33]. As an alternative to the adipokine hypothesis, other adiposity-related factors may in part explain the relationship between central body fatness and arterial stiffness. These include low-grade systemic inflammation [14,27,34] and endothelial dysfunction [14,35].

These potential mechanisms might (partly) explain the relation between (abdominal) obesity and arterial stiffness, and therefore we investigated these mechanisms in this thesis.

Amsterdam Growth and Health Longitudinal Study

The study design of the present thesis has been developed within the ongoing *Amsterdam Growth and Health Longitudinal Study* (AGAHLS), an observational longitudinal study that started in 1976 with a total inclusion of 698 boys and girls [36-38]. Its initial goal was to describe the natural development of growth, health and lifestyle of adolescents, and to investigate longitudinal relationships between biological and lifestyle variables. The mean age of the subjects at the beginning of the study was 13.1 (± 0.8) years. Since then, subjects have been measured 3 to 9 times during a 30-year follow-up period. At each measurement, anthropometrical,

biological and lifestyle variables were assessed, as detailed elsewhere [36-38]. In 2000, when the subjects' mean age was 36.6 (± 0.6) years, the following measurements were added to the study for the first time: body composition (including body fat distribution) by means of dual-energy x-ray absorptiometry (DXA) and properties of three large arteries by non-invasive ultrasound imaging (Figure 1).

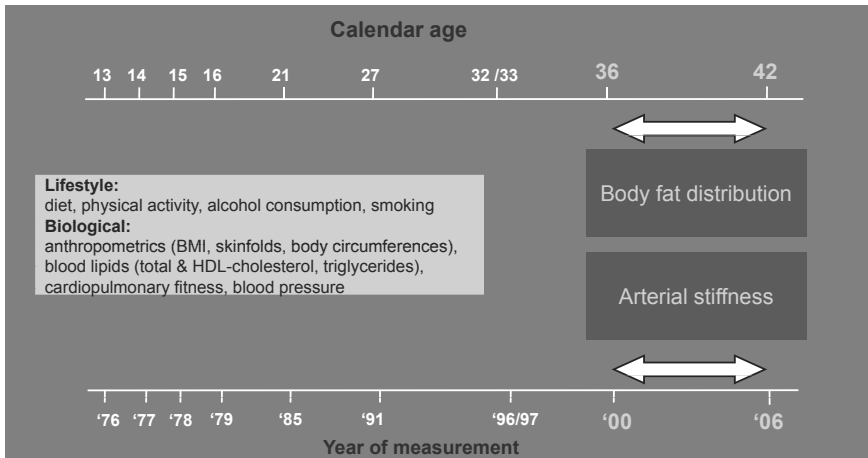


Figure 1. The Amsterdam Growth and Health Study design.

Objectives and outline of this thesis

Previously, it was unknown whether obesity-related vascular pathology also manifests itself in vessel wall alterations, and at what stage of life these changes could become apparent. Over the last years, studies that were mostly cross-sectional in design have shown (central) obesity to be independently related to increased arterial stiffness [39-41]. In addition, previous data from the AGAHL cohort, which consists of apparently healthy participants, demonstrated cross-sectionally that such effects can be detected relatively early in life (at a mean age of 36 years) [42,43]. At this age, 1.1% of the participants were underweight ($BMI < 18.5 \text{ kg/m}^2$), 65.3% normal weight ($BMI 18.5-25.0$), 28.5% overweight ($BMI 25-30$) and 5.1% obese ($BMI > 30$). This implies that obesity-related effects in arterial stiffness are not confined to individuals with overweight or obesity, but are seen across the entire range of levels of body mass/fatness. However, prospective studies on the effects of body fat

(distribution) on vessel wall properties as well as potential mechanistic insights into these associations in young, apparently healthy adults are limited.

Therefore, in the present thesis, we investigated the (longitudinal) association between body fatness, fat distribution and arterial stiffness, and in addition, we investigated a few candidate pathophysiological mechanisms of this relationship. Specifically, we formulated the following main research questions (as illustrated in Figure 2):

1. What are the associations of body fatness and body fat distribution, and changes herein during a 6-year follow-up, with (changes in) arterial stiffness?
2. Are these associations mediated by biomarkers of low-grade inflammation (i.e., C-reactive protein, serum amyloid A, interleukin 6, interleukin 8, tumor necrosis factor α and soluble intercellular adhesion molecule 1), and/or biomarkers of endothelial dysfunction (i.e., soluble endothelial selectin, thrombomodulin and both vascular- and intercellular adhesion molecules 1 and von Willebrand factor)?
3. Are these associations (from research question 1) mediated by adipokines (i.e., leptin, adiponectin)?

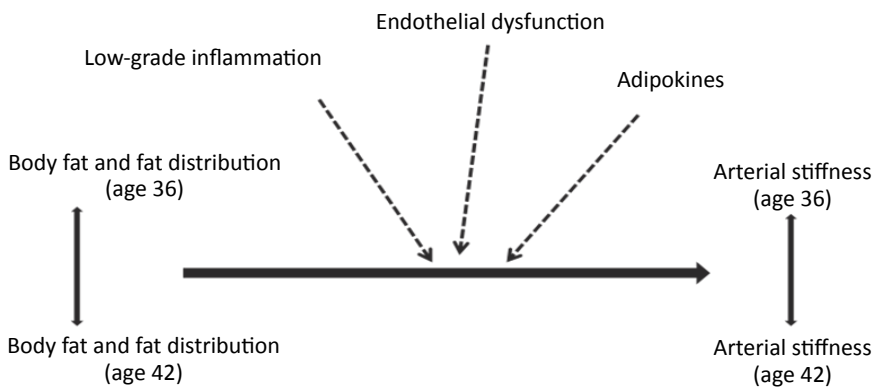


Figure 2. Illustration of the hypothesized associations investigated in this thesis.

In order to answer the above research questions, the outline of this thesis is as follows:

Chapter 2 addresses the associations between changes in central (i.e. trunk) fat versus peripheral (i.e. limbs) fat and lean masses with changes in arterial stiffness over a 6-year follow-up period.

In **Chapter 3**, we investigated the associations between, on the one hand, biomarkers of endothelial dysfunction (i.e., soluble endothelial selectin, thrombomodulin and both vascular- and intercellular adhesion molecules 1 and von Willebrand factor) and of low-grade inflammation (i.e., C-reactive protein, serum amyloid A, interleukin 6, interleukin 8, tumor necrosis factor α and soluble intercellular adhesion molecule 1) and, on the other hand, arterial stiffness, over a 6-year period.

Chapter 4 addresses the associations between leptin, adiponectin, and the leptin-to-adiponectin ratio (LAR) with arterial stiffness, over a 6-yr period.

In **Chapter 5** we investigated to what extent levels of adipokines (adiponectin, leptin, the leptin-to-adiponectin ratio (LAR)), biomarkers of low-grade inflammation and endothelial dysfunction explain the relationship between central fatness and arterial stiffness over a 6-year period.

In **Chapter 6** we studied to what extent the longitudinal development of fatness parameters (BMI, sum of skinfolds and skinfold ratio) from the age of 13 to 36 years precede favourable or unfavourable levels of adipokines at the age of 36 years. In addition, we investigated if we could identify a certain critical age/period in which the groups with favourable and unfavourable levels of adipokines began to differ substantially.

Finally, in the general discussion in **Chapter 7**, the main findings of the studies included in this thesis are discussed, including some methodological issues. Furthermore, the practical implications and suggestions for future research are addressed.

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