

## COMMENTARY

# Increased visceral adipose tissue rather than BMI as a risk factor for dementia

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## Abstract

In addition to the association between overweight/obesity and cardiovascular disorders, with the presence of a vascular burden as a cofactor, recent studies have particularly focused on the association between indicators of adiposity and dementia. Particularly, renewed predictive value has been addressed to body mass index (BMI). A high BMI can increase the risk for dementia when measured before clinical dementia onset. Although the use of BMI in population-based and clinical studies is feasible, this is an index of weight excess and shows limits in its ability to distinguish between fat and fat-free mass or between deep (visceral) abdominal fat and subcutaneous abdominal fat. In this scenario, we suggest that visceral adipose tissue (VAT) rather than BMI should be considered as a concurrent factor in the development of dementia. Several physiopathologic theories (neurochemical, hormonal, atherosclerotic and inflammatory) have been proposed to explain the decline of cognitive functions. Along with this, well known cardiovascular risk factors (dyslipidaemia, insulin resistance, blood pressure, adipocytokine/chemokines, atherosclerosis) contributing to the development of cognitive decline seem more strongly related to body fat distribution, particularly visceral adipose tissue (VAT), rather than to BMI. With this regard, VAT may be reasonably considered to play a predominant role.

**Keywords:** dementia, cognitive decline, body mass index (BMI), visceral adipose tissue, elderly

## Introduction

Dementia is a clinical state of severe cognitive impairment that likely reflects the summed effects of multiple pathological processes associated with advanced ageing.

Recently, particular attention has focussed on the presence of a longitudinal link between middle-age adiposity [1, 2] and later-life obesity [3, 4] and the decline in cognitive function. Thus, obesity seems responsible for further health implications besides cardiovascular disorders (CVD), and the presence of a vascular burden is nowadays recognised as a possible common cofactor in the development of dementia [2]. The recent systematic review by Gorospe and Dave [1] supports the hypothesis that an increased body mass index (BMI) is independently associated with an increased risk of dementia. Though, as the authors themselves have pointed out, the mechanisms underlying this relationship are still unclear [1].

Recent preliminary studies suggest that the role of abdominal obesity should deserve further investigation [2–4].

In this commentary, we wish to point out the advantages and disadvantages of BMI compared to visceral adipose tissue (VAT) and to emphasise that VAT rather than BMI may be the risk factor for dementia.

Although BMI is widely accepted as a simple marker of adiposity in population-based studies, and is recognised as an instrument to diagnose obesity for all age-groups (BMI  $\geq 30$  kg/m<sup>2</sup>), it should be more properly seen as an index of weight excess, rather than body fatness. The disadvantage of BMI measurement is that it does not provide information on body composition or distinguish between fat and fat-free mass or between deep (visceral) abdominal fat and subcutaneous abdominal fat. Along with this neurochemical, hormonal, inflammatory molecules and vascular factors implicated in cognitive decline are related

to adipose tissue distribution (and in particular VAT) rather than to general measures of overweight/adiposity (BMI).

An example of how VAT, instead of BMI, is involved in the determination of cognitive decline is provided by the analysis of specific vascular (atherosclerosis and blood pressure) and metabolic risk factors (insulin resistance and hyperglycaemia).

Atherosclerosis is considered among the possible factors involved in the development of both vascular dementia and Alzheimer's disease (AD) and a physiopathological model based on multiple asymptomatic brain injuries related to peripheral vascular disease has been proposed [5].

Regardless of BMI, patients with increased intra-abdominal fat usually have an atherogenic lipid profile, high fasting serum glucose and insulin levels and high blood pressure, all metabolic factors participating in the atherosclerotic process. These factors in turn contribute to the occurrence of coronary heart disease, stroke, as well as peripheral vascular diseases [6–8].

Several studies report that blood pressure, decades before the onset of the cognitive decline, can play a role in the determination of dementia but the exact underlying mechanisms are not fully explained [2, 5, 9, 10]. Some studies have demonstrated that a higher systolic blood pressure is associated with an increased risk for Alzheimer's disease and vascular dementia in the elderly, probably due to artery stiffness and severe atherosclerosis [9]. Hypertension is also a risk factor for stroke and contributes to the development of white matter hypertensive lesions on brain MRI studies. Other analyses have shown an inverse association with low diastolic levels, particularly in patients taking antihypertensive medications, and in whom poor cerebral perfusion has been singled out as the responsible factor [10]. It is worth noting that VAT has been indicated as the most important contributor to hypertension, and indices of abdominal fat deposition have been demonstrated as more significantly related to high blood pressure than BMI [7]. In addition, hypertension is a risk factor frequently associated with insulin resistance (IR) [7, 8].

Diabetes, metabolic syndrome and more widely IR have been included among the strongest factors involved in the association between the decline of cognitive function and BMI [2, 11, 12]. The metabolic syndrome is a cluster of factors (abdominal obesity—described by waist circumference—hypertriglyceridaemia, low- and high-density lipoprotein level, hypertension and fasting hyperglycaemia) and a commonly accepted precursor to diabetes. Both these conditions have been demonstrated as significantly associated to vascular disease [7, 8, 13]. With regard to the implications of visceral adiposity in health and disease, recent investigations show that intra-abdominal fat accumulation, rather than BMI, is a significant independent predictor of the IR, impaired glucose tolerance and dyslipidaemia seen in both metabolic syndrome and diabetes [6, 7]. There is general agreement that VAT affects IR and glucose metabolism through a higher rate of basal lipolysis and free fatty acids (FFAs) overflow to the liver [14]. However, the excess of systemic FFA availability is related to overall

upper-body fat (visceral and non-visceral) [14]. Although no direct link has been demonstrated so far between FFAs and cognitive decline in humans, *in vitro* studies suggest that an increased availability of FFAs is associated with more pronounced molecular and histopathological degeneration of neurons [15]. Also, hyperinsulinaemia is a frequent correlate of expanded VAT [6, 7]. Accordingly, the direct action of insulin on brain structures has been considered among the possible physiopathological factors involved in the development of dementia [2, 3]. Furthermore, IR represents a model of systemic chronic low-grade inflammatory background [7, 16].

An atherosclerotic model of systemic inflammation, similar to the one suggested for CVD, was also proposed to explain the higher cognitive impairment in these subjects having higher plasma levels of inflammatory markers (e.g. C-reactive protein, interleukin 6) [2, 11, 17].

Nowadays, adipose tissue should be considered as the largest endocrine organ, and it is well known that the intra-abdominal compartment is metabolically more active as a source of cytokines, chemokines and hormone-like proteins, such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1) and the newly isolated protein, visfatin [16].

Quantitative measurements of the abdominal fat depot, in uncomplicated obesity, appear to account far more than BMI (strong correlation) for the circulating levels of several of these molecules (C-reactive protein, MCP-1, IL-6, soluble IL-6 receptor, TNF- $\alpha$  and soluble TNF receptor-I) and indicate VAT as the main contributor [18, 19]. This hypothesis is confirmed by several genetic studies showing higher mRNA expression and protein release of these mediators [16]. Most of them exert an action of inflammatory pathway activators both at the site of fat distribution (paracrine action) and also systemically (endocrine action) [16]. This contributes to the possible relationship between VAT and an increase of CVD risk [6, 16, 18, 19]. Thus, the role of both central obesity and the systemic action of VAT products has been proposed as factors affecting brain health and subsequent cognitive decline.

## Conclusions and Perspectives

BMI, as a readily available measure of weight excess, seems to be a good predictor of both vascular dementia and AD [1, 2, 5, 9, 20], but this measure is limited by the lack of information on body composition and the distribution of body fat. Moreover, factors known to be involved in the development of both vascular dementia and AD such as, hypertension, insulin resistance, pro-inflammatory molecules (adipocytokine-cytokine), and atherosclerosis seem more strongly related to body fat distribution, particularly VAT, rather than to BMI. However, VAT quantification implies imaging techniques and does not fit in a clinical setting as easily as BMI. There are, however, anthropometric surrogates, such as waist circumference (WC), waist-to-hip and waist-to-height ratios

(WHR and WHtR, respectively) which are readily available and are routinely used by nutritionists, diabetologists, endocrinologists and cardiologists. Although limitations due to poor reproducibility (e.g. variability in landmarks) have been pointed out, the routine measurement of waist and hip circumference and height is feasible and the use of anthropometric indicators would be also conceivable in a neurological setting.

Future prospective studies may confirm whether VAT and its surrogate measures (WC, WHR, WHtR) actually are a risk factor for cognitive decline. Probably, focusing attention on the pathologic distribution of adipose tissue, rather than on the presence of overt obesity alone, may provide an additional evidence for VAT implications in an inflammatory-atherosclerotic model of cognitive decline. In this respect, it will be also interesting to compare whether the pathological distribution of adipose tissue most strongly correlates with AD compared to vascular dementia, considering the different contributions of small vessel disease to the former compared to the latter, in which genetic risk should be considered.

In any case, the relationship between BMI and dementia does not seem to be a simple one. Some authors have shown that it is most likely a J-shaped curve, where a low BMI represents a strong risk factor [4, 20]. In some cases, this association may be the result of weight loss, which might have masked the detrimental effects of increased visceral adiposity in middle age [4, 21]. In others, no certain cause has been demonstrated so far, although hyperinsulinaemia has been singled out as a possible contributor [4]. Thus, when addressing underweight people, the use of anthropometric surrogates alone is an obvious limitation, while that of BMI as well as of body weight history still conserves a great value. For decades, BMI has been used as a simple indicator of nutritional status in most countries. Thus, it will take a long time before anthropometric data becomes available in the routine clinical setting.

## Key points

- Growing evidence supports the idea that an increased body mass index (BMI) is a risk factor for dementia. However, the mechanisms underlying this relationship still need to be explained.
- Several physiopathological theories (neurochemical, hormonal, atherosclerotic and inflammatory) have been proposed to explain the decline of cognitive functions.
- Interestingly, many of the vascular (hypertension, atherosclerosis), inflammatory (adipocytokine-cytokine) and metabolic factors (insulin resistance, fasting hyperglycaemia) contributing to the development of cognitive decline seem more strongly related to body fat distribution, particularly the visceral adipose tissue (VAT), rather than to BMI.

- In this regard, we suggest that VAT instead of BMI might therefore be considered as a risk factor for cognitive decline.

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