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SPOTLIGHT REVIEW

The molecular mechanisms of obesity paradox

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Abstract Clinical observations suggest a complex relationship between human obesity and cardiovascular disease. Whilst abdominal (visceral) adiposity leads to deleterious metabolic disturbances, subcutaneous fat accumulation has a benign effect on cardiometabolic risk. Notably, an accumulating body of evidence paradoxically links increased body mass index with a better prognosis in patients with established cardiovascular disease, a finding that has been termed the 'obesity paradox'. Whilst this is now acknowledged to be an epidemiological finding, a metabolically healthy obese group associated with low cardiovascular risk has also been identified. The current concept of adipose tissue (AT) biology suggests that AT expansion is feasible without accompanying adipocyte dysfunction. A metabolically healthy obese phenotype can be promoted by exercise, but is also linked with intrinsic AT molecular characteristics such as efficient fat storage and lipid droplet formation, high adipogenesis capacity, low extracellular matrix fibrosis, angiogenesis potential, adipocyte browning and low macrophages infiltration/activation. Such features are associated with a secretomic profile of human AT which is protective for the cardiovascular system. In the present review, we summarize the existing knowledge on the molecular mechanisms underlying the 'obesity paradox' and whether fatness can be healthy too.

Keywords Obesity • Adipose tissue • Body mass index • Adiposity • Cardiorespiratory fitness

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1. Introduction

Obesity has traditionally been regarded as a risk factor for cardiovascular disease (CVD), even though the direct relationship between obesity and coronary atherosclerosis in autopsy and angiographic studies is rather weak.[1] The obesity-CVD relationship is indeed a complex one.[2] Abdominal obesity leads to well-identified disturbances in adipocyte biology and adipose tissue (AT) inflammation with direct systemic metabolic consequences. The latter include dysglycaemia and insulin resistance, alterations in lipid metabolism and blood pressure regulation that mutually favour endothelial dysfunction and atherogenesis.[2] Nonetheless, subcutaneous fat accumulation in the thighs or hips has little or no effect on CVD risk,[3] suggesting that the anatomical location of fat may indicate differences in the developmental origin, patterning genes and micro-environmental factors among human AT depots decisive for their relationship to cardiovascular physiology.[4]

Indeed, the role of obesity as an independent risk factor for coronary atherosclerosis has been strongly challenged over the recent years[5] mainly due to epidemiological data suggesting better cardiovascular outcomes in obese patients with established CVD.[6] Whilst in primary prevention settings, higher body mass index (BMI) independently predicts increased cardiovascular morbidity, in patients with heart failure or coronary heart disease higher BMI is paradoxically associated with lower risk for future cardiovascular events.[2] The popular debate over this 'obesity paradox'[5] is perplexed by the inherent limitations of observational studies and the BMI as an obesity index.[2] Whilst the 'obesity paradox' is acknowledged to be an epidemiological finding, within obese individuals a subgroup has been identified that lacks the obesity-related metabolic abnormalities and is associated with low cardiovascular risk.[7–9] Identification of 'low-risk' obese individuals is vital, but this attempt is perplexed by the two-way communication of AT with the cardiovascular system[10–13] which implies that changes in AT phenotype could be also the result of vascular disease.

In order to establish causal links between adiposity and CVD, interpret the 'obesity paradox' and uncover potential therapeutic targets, an understanding of the core modifications of AT biology and changes in its secretome as a consequence of fat expansion is required. Focusing on the quintessential player of obesity i.e. the adipocyte could help to comprehend the role of obesity in CVD. Therefore, the scope of the present review article is to summarize the recent knowledge on obesity-related mechanisms of CVD and whether fatness can be healthy too.

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2. The notion of obesity paradox in clinical studies

Whilst several obesity indices exist, the one most commonly employed by clinical studies is BMI, given that it can be quickly and reliably measured. In published literature there is a well-established J-shaped association between BMI and mortality in the general population, supported by ample clinical evidence including a recent meta-analysis in 3.74 million subjects.[14] Early follow-up periods and inclusion of smokers tend to change this relationship towards a U-shaped format (possibly due to smoking-related comorbidities and/or cachexia and cancer-related deaths in the lowest BMI group). Another meta-analysis on more than 10.6 million individuals in 4 different continents has reported similar results,[15] namely increased mortality risk for BMI levels either below or above the optimum 20.0–25.0 kg/m^2 range. The association of BMI >25.0 kg/m^2 with increased mortality risk is more pronounced in male and younger individuals.[15] In type 2 diabetic patients, the optimum BMI is reportedly slightly higher, i.e. in the range of 28.0–30.0 kg/m^2, and non-linearly increases above that range.[16]

These studies support an unequivocal link of obesity (as measured by BMI) with increased mortality in the general population.[14–16] Conversely, clinical studies in patients with established CVD have paradoxically reported a better outcome of obese individuals.[17,18] Initially, it was observed that obese patients with systolic heart failure[18] or post-percutaneous coronary intervention[17] have a better prognosis and the term 'obesity paradox' was coined to describe this association. Since then an obesity paradox has been reported in overweight patients (BMI range of 25.0–30.0 kg/m^2) with stable coronary heart disease[19], acute coronary syndromes,[20,21] or patients undergoing coronary artery bypass grafting.[22] Notably, the relationship between BMI and mortality in CVD patients remains still U-shaped, but the nadir of mortality risk seems to be observed at higher than the recommended BMI levels, i.e. in the overweight range (*Figure 1A*). Higher BMI levels in the obesity range (BMI > 30 kg/m^2) have not consistently been associated with a better prognosis.[2] Other groups have opposed the notion of protective obesity in stable coronary patients.[23] Nonetheless, ample epidemiological evidence now supports the presence of an 'obesity paradox' in patients with established CVD.[2]

3. Is excess adiposity protective? The obesity paradox revisited

How can these epidemiological findings be interpreted? Could it be supported that excess adiposity is beneficial for patients with established CVD? Before jumping to conclusions several facts should be considered.

First and foremost, it should be clarified that the notion of 'obesity paradox' has been fabricated by the 'BMI paradox', i.e. the association of elevated BMI with better outcomes. The observed epidemiological associations could be biased by several limitations inherent to clinical studies (reverse causality, selection bias, inadequate follow-up periods, the selection of the reference BMI group, etc.) and cannot support causality.[2] Other limitations are related to the use of BMI *per se* as an obesity index, which does not take into account body fat distribution or distinguish body lean mass from fat mass.[24]

Interestingly, when other indices are used to define obesity, no 'obesity paradox' is observed. For example, central obesity (which cannot be captured by BMI) is strongly associated with the risk of CVD development and total mortality in the general population.[25] In patients with coronary heart disease waist circumference (WC) and waist-to-hip ratio (WHR), which are both indices of abdominal adiposity, are independently linearly associated with increased mortality risk[26] (*Figure 1B*), and provide additive predictive value (over BMI) for the outcome of these patients.[27] Other measures of body fat distribution, such as waist-to-height ratio (WHtR) and waist-to-hip-to-height ratio (WHHR) are also strong independent predictors of cardiovascular and all-cause mortality risk.[28,29] Increased body fat percentage (BF%), i.e. excess adiposity, also increases the risk for metabolic traits, and is independently associated with increased mortality risk.[30] In patients with established CVD, the association between BF% with clinical outcomes seems to be strongly influenced by body composition and lean body mass. Increased lean body mass index is independently associated with lower mortality risk in heart failure[31] or stable coronary[32] patients. Particularly in heart failure, patients with both low lean mass index and low BF% are an exceptionally high-risk group,[31] a finding possibly reflecting the advanced disease state and the presence of cardiac cachexia.

Imaging studies have also contributed to clarifying the perplexities generated by the notion of the 'obesity paradox'. Volumetric analyses of body fat depots in either computed tomography or magnetic resonance imaging studies have uncovered distinct associations of diverse AT depots with CVD risk.[2,33] For example, subcutaneous AT volume[34] or lower body fat[35] are modestly or even negatively associated with CVD risk. Conversely, visceral (abdominal)[36] and epicardial/pericardial[33] AT volumes predict increased CVD risk in primary or secondary prevention settings. Intramuscular fat accumulation (a marker of systemic insulin resistance) is also an independent predictor of CVD risk in males,[34] whilst other patterns of ectopic fat accumulation (i.e. presence of fat in locations not classically associated with fat storage) may be important too. For example, bone marrow fat content affects systemic metabolism[37], whilst fatty liver content is independently associated with insulin resistance[38] and possibly also to CVD risk, even though robust prospective clinical data are still lacking. The definitions of the various obesity indices and their associations with CVD risk are summarized in *Table 1*.

In summary, the notion of the obesity paradox appears to be an epiphenomenon of the use of BMI to describe obesity. It applies only to mildly overweight (and not morbidly obese)[2] individuals and is not observed when other indices of obesity (anthropometric[26] or imaging[36]) are used. Conclusively, it is now well accepted that visceral adiposity is positively associated with CVD risk, but subcutaneous fat accumulation is modestly or even negatively related to cardiometabolic and mortality risk. The basic facts on the 'obesity paradox' are summarized in *Table 2*.

4. The metabolically healthy (but) obese phenotype

Whilst the 'obesity paradox' seems to be an epidemiological finding associated with the limitations of BMI, clinical evidence suggests that a subgroup of obese individuals (defined either by BMI or BF% criteria) is indeed characterized by low CVD risk. In an eloquent study Ortega et al.[8] assessed 43 265 adults for cardiorespiratory fitness (CRF, by treadmill exercise test) and obesity (by BF%). It was shown that metabolically healthy obese (MHO) individuals (i.e. obese but no criteria met for metabolic syndrome) had significantly better fitness status compared to non-MHO individuals (also termed metabolically abnormal or unhealthy obese). Moreover, the MHO group had 30–50% lower risk for all-cause mortality and CVD compared to non-MHO, similar to that of metabolically healthy normal weight subjects.[8]

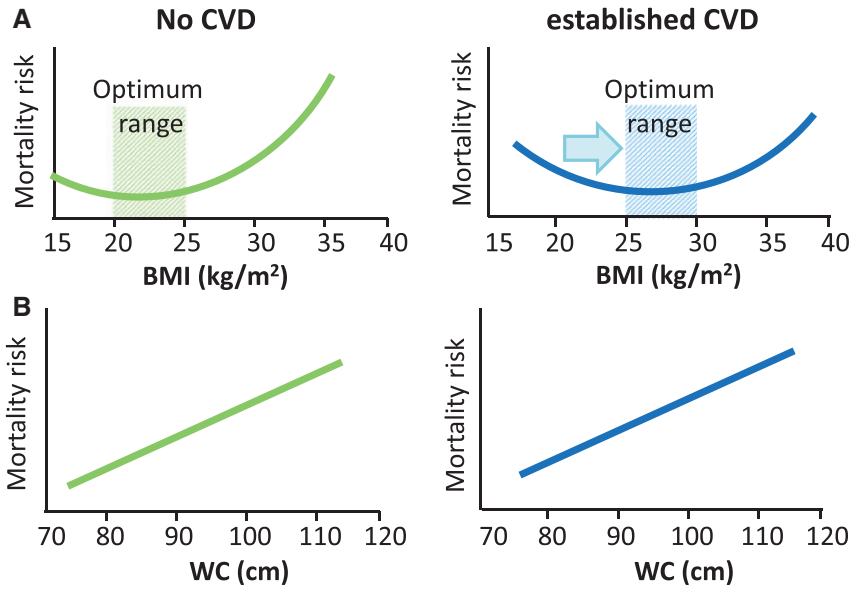

Figure 1 Association among body mass index, waist circumference, and mortality risk. (A) Body mass index (BMI) has a J- or U-shaped relationship with mortality risk in individuals free of cardiovascular disease (CVD). In these subjects, the optimum BMI range associated with lowest mortality risk is between 20 and 25 kg/m^2. Nevertheless in patients with established CVD, the nadir in mortality risk is observed with higher BMI values (25–30 kg/m^2). (B) This obesity paradox is not observed by the use of waist circumference as an obesity index (bottom panels), which is linearly associated with mortality risk in both healthy subjects and CVD patients.

This is not unexpected since fitness is a well-established independent predictor of CVD risk and total mortality.[39,40] Landmark studies in the field[41,42] have demonstrated that having good fitness levels (usually defined as not belonging in the bottom age- and sex-adjusted quintile of CRF levels) reduces mortality risk by 44%.[41] Indeed being fit seems to be more important than losing weight in terms of lowering CVD mortality risk according to studies with long-term follow-up.[42] In the landmark Aerobics Center Longitudinal Study in 14 345 men every 1-MET improvement in CRF was associated with 15% and 19% lower risk of all-cause and CVD mortality.[42] Taking into account CRF levels significantly improves the predictive value of statistical models for short- and long-term CVD risk.[43] Interestingly, unfit obese subjects have almost twofold higher CVD risk compared to obese but fit individuals,[7] whilst the latter have lower CVD risk compared to normal weight but unfit individuals[7] (the '*fat but fit*' hypothesis). Notably, in a cohort of 9563 male CHD patients, an 'obesity paradox' was documented across categories of BMI, BF% and WC only in men with low levels of CRF.[44] Therefore, varying fitness levels across BMI subgroups could partly explain the epidemiological findings related to the 'obesity paradox'.

Several mechanisms could account for the low CVD risk of the 'fat but fit' individuals. Exercise has numerous important beneficial effects that are associated with whole body health (e.g. maintenance of muscle mass and skeletal health, increased resting metabolic rate, better mood and sleeping patterns, less psychological stress).[40,45] Being fit seems also important to counteract the metabolic perils of obesity.[8] CRF lowers the risk for developing any of the components of metabolic syndrome and confers beneficial effects to cardiovascular system including benefits in blood pressure regulation, heart rate variability, myocardial oxygen demand, endothelial function and systemic inflammation.[40] MHO individuals, possibly as a result of being fit,[8] have also lower visceral adiposity and systemic insulin resistance,[40] which could explain the lower CVD risk of this group.[7] This is also supported by the observation that lean but unfit individuals are at increased risk for developing metabolic syndrome compared to fat and fit subjects.[8]

Despite its value for risk-stratification purposes, the proposal of MHO has not been unanimously adopted because (i) MHO definition criteria are not consistent across the literature, (ii) MHO patients often transit from a healthy to an unhealthy phenotype,[46] and (iii) the survival benefit of MHO group compared with metabolically healthy normal-weight individuals is not a consistent finding, particularly in studies with longer follow-up periods.[7,8]

Nonetheless, the persistent search for a healthy obesity phenotype is important since it relates to the deployment of CVD prevention measures affecting a large proportion of the general population. It is currently estimated that the prevalence of the MHO is close to 12% of obese individuals (or 7 million of European adults).[9] Obese individuals (by BMI or BF%) with one of the following criteria: (i) no metabolic abnormalities (based on metabolic syndrome criteria), (ii) no insulin resistance (based on homeostatic model assessment, quantitative insulin sensitivity check index or hyperinsulinemic–euglycaemic clamp measurements), (iii) high CRF levels (based on maximal oxygen consumption during exercise treadmill test or muscle strength which is also a good surrogate), (iv) low visceral AT volume (by imaging), and possibly also (v) low levels of systemic inflammatory mediators could be classified as MHO.

5. A molecular understanding of benign adiposity

Further to the aforementioned criteria, the molecular phenotyping of AT could also contribute to the identification of a 'low-risk' adiposity or MHO phenotype. AT secretomic profile, regional fat distribution and

Table 1 Established and newly introduced anthropometric and imaging indices of obesity and their relationship with cardiovascular disease risk

Obesity Index	Definition	Cut-off values[a]	What does it measure?	Relationship with cardiovascular disease risk
Anthropometric indices				
Body Mass Index (BMI)	Weight adjusted for height weight (kg)/height^2 (m^2)	<18.5 lean, 18.5–24.9 normal, 25.0–29.9 overweight, 30.0–34.9 class I obesity, 35.0–39.9 class II obesity, ≥40.0 class III obesity	Body mass in relation to height of an individual. Does not distinguish between lean or body fat mass.	J- or U-shaped associations with mortality and CVD risk in healthy individuals; paradoxically inversely associated with mortality risk in patients with established CVD. Moderate associations with CVD risk compared with abdominal obesity indices
Waist circumference (WC)	WC is measured at a level between the lowest rib and the iliac crest (or practically the smallest circumference of the natural waist)	Men: WC > 102 cm (40 in) Women: WC > 88 cm (35 in)	Index of central (abdominal) obesity	Positive linear relationship with CVD risk in primary and secondary prevention settings
Waist-to-hip ratio (WHR)	WHR equals the WC divided by the hip circumference (measured at the level of widest circumference over the greater trochanters)	Males ≥0.90 Women ≥0.85	Index of abdominal obesity and gynoid body fat distribution	Positive linear relationship with CVD risk in primary and secondary prevention settings (stronger predictor in women than men)
Waist-to-thigh ratio (WTR)	The WTR equals the WC divided by the thigh circumference	Not established	Index of abdominal obesity (adjusted for the thigh circumference)	Positive linear relationship with CVD risk in primary and secondary prevention settings in both sexes
Waist-to-hip-to height ratio (WHHR)	The WHHR ratio equals the WHR divided by height	Not established	Index of abdominal obesity further adjusted for the height of an individual (improved description of body fat distribution vs. WC or WHR)	Positively associated with cardiometabolic risk. Provides independent and additive predictive value and improved discrimination for CVD (over other obesity indices)
Waist-to-height ratio (WHtR)	The WHtR equals the WC divided by height	0.5 for both sexes (but not widely validated)	Index of abdominal obesity adjusted for the height of an individual to better reflect body fat distribution	More sensitive marker than BMI for increased cardiometabolic risk, independently linearly associated with CVD and mortality risk (better performance than WHR/WC/BMI)
A Body Shape Index (ABSI)	WC (cm) × BMI$^{0.66}$ × height (m)$^{0.5}$	Not established	Index of abdominal fatness (increased WC) adjusted for BMI and height	In general population independently associated with CVD and mortality over and above BMI or WC
Sagittal abdominal diameter (SAD)	the distance between the back and the highest point of the abdomen (supine position)	<25 cm normal/>30 cm increased risk (not widely validated)	Index of abdominal obesity	Positive linear association with CVD risk independently of BMI. Incremental value over other abdominal indices poorly studied.
Body adiposity Index	Hip circumference (cm)/((height (m)$^{1.5}$)-18)	Not established	Index of body fat distribution	Moderate positive associations with CVD risk, less strong though compared to other obesity indices
Body Fat percentage (BF%)	Measured by hydrostatic weighing, predicted by body skinfolds measurements or by DXA whole body scans	>25% in men and > 30% in women (not widely validated, depends on age)	The percentage of the body mass corresponding to fat mass	J-shaped relationship with CVD and mortality risk independently of BMI

Continued

Table 1 *Continued*

Obesity Index	Definition	Cut-off values[a]	What does it measure?	Relationship with cardiovascular disease risk
Imaging biomarkers of body adiposity				
Trunk volume to leg volume	Ratio of trunk and leg volumes as measured by DXA scan output	Not established	Composite index of body adiposity distribution and lean mass	Independently positively associated with mortality risk in general population, over BMI, and WC
Visceral AT volume	Quantification of abdominal visceral AT volume by CT image analysis above S1 level (in a single or multiple axial slices)	Not established	Surrogate marker of visceral adiposity	Positively associated with CVD over and above BMI
Subcutaneous AT volume	Quantification of abdominal subcutaneous AT volume by CT/MRI analysis (usually in combination with VAT in a single or multiple axial slices)	Not established	Surrogate marker of subcutaneous adiposity	No associations with CVD or mortality risk
Epicardial/pericardial AT volume	Quantification of epicardial AT volume by cardiac CT/MRI (fat located inside the pericardial sac)	Not established	Surrogate marker of ectopic visceral (cardiac) adiposity	Independently associated with CVD and mortality risk
Periaortic AT volume	Quantification of the AT volume surrounding the thoracic or abdominal aorta by CTA/MRI imaging. Boundaries not appropriately defined.	Not established	Surrogate marker of perivascular adiposity	Positively associated with aortic plaque burden; no established associations with CVD risk
Pericoronary AT volume/depth	Quantification of the AT mass surrounding the coronary arteries (thoracic or abdominal) aorta by CTA. Boundaries not appropriately defined	Not established	Marker of coronary perivascular adiposity	Associated with coronary plaque burden; no established associations with CVD risk
Liver fat content	Quantification of the degree of liver fatty infiltration by CT, MRI or MRS	Not established	Marker of ectopic adiposity, strongly associated with abdominal visceral adiposity	Associated with systemic insulin resistance; no established associations with CVD risk

[a]Universal cut-off values may not be applicable to certain ethnic groups. AT, adipose tissue; CVD, cardiovascular disease; CT, computerized tomography; CTA, CT angiography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

Table 2 Basic facts about the 'obesity paradox'

- The obesity paradox is linked with the use of body mass index (BMI) as an obesity index. Other indices of obesity (e.g. WHR) have not been associated with the 'obesity paradox'
- In the general population there is a 'U-shaped' or 'J-shaped' relationship of BMI with cardiovascular disease risk
- In patients with heart failure or coronary heart disease increased BMI is paradoxically associated with better outcomes. This applies mainly to overweight and obese (but not morbidly obese) individuals
- A similar paradoxical relationship of increased BMI with better prognosis has been also observed in other disease conditions (e.g. sepsis, chronic pulmonary diseases, etc.)
- Not all clinical studies support the notion of obesity paradox in cardiovascular disease
- The obesity paradox could be explained by the inherent limitations of both BMI and clinical studies

the distinct biology of human fat depots, adipocyte turnover and the type of AT expansion (hyperplasia vs. hypertrophy), extracellular matrix (ECM) fibrosis and stiffness, angiogenesis potential, adipocyte browning, the degree of macrophage infiltration, endogenous AT immune responses and local cross-talk paracrine mechanisms (e.g. between epicardial AT/myocardium or perivascular AT/vessels) have emerged as important features of AT health in obesity.

5.1 AT secretomic profile in obesity

Obesity by high-fat feeding in experimental animal models leads to upregulation of pro-inflammatory cytokines, chemokines, and activation of toll receptor-signalling pathways in AT, leading to adverse AT adaptations.[47] Human obesity is also associated with an imbalance in adipokines released into systemic circulation. Increased body fat mass is inversely associated with adiponectin biosynthesis, an adipokine with well-characterized insulin sensitizing properties,[48] anti-oxidant and anti-inflammatory effects on cardiomyocytes,[12] vascular smooth muscle, and endothelial cells.[11,13] Conversely, plasma levels of pro-atherogenic adipokines, such as leptin and resistin, are positively correlated with body adiposity. Leptin promotes vascular smooth muscle cell hypertrophy, negatively affects eNOS function and NO bioavailability and its upregulation in obesity could partially explain the obesity-related CVD risk.[48] Other pro-inflammatory mediators such as CCL2, TNF-a, interleukin-18,[49] ANGPTL2, and WNT5A[50] are also upregulated in the visceral AT of obese individuals and can synergistically promote insulin resistance, metabolic dysfunction and vascular disease development via endocrine/paracrine effects.[48]

5.2 Regional fat distribution

The location/regional distribution of fat critically determines the overall effects of obesity on cardiometabolic health,[36,51] an observation encapsulated in the traditional knowledge about 'apple' vs. 'pear'-shaped obesity.[3] Differences in the strength of association of human AT depots mass with CVD[36,51] could stem from the completely different properties of subcutaneous compared with visceral adipocytes.[52] Our studies in CHD patients have demonstrated that human subcutaneous AT contains larger adipocytes, has lower infiltration by $CD68^+$ and M1 activated cells, and expresses higher levels of cardioprotective adipokines, such as adiponectin[10] (although these findings may not apply to all obese individuals). Subcutaneous adipocytes have distinctly different gene expression patterns (higher adiponectin expression and lower expression of pro-inflammatory adipokines),[52] are better differentiated, and have increased adipogenesis and browning potential[53,54] compared with visceral adipocytes. Human AT depots also differ in their intrinsic hematopoeitic stem cell activity of the stromal-vascular fraction (with that of visceral being lower than of subcutaneous), which may affect AT immuno-metabolism and inflammatory cell infiltration in obesity and diabetes.[55] Such differences between subcutaneous and visceral adipocytes, which may relate to intrinsic differences in the respective precursor cells and their stromal-vascular fraction,[52] could partly explain why subcutaneous adiposity is not paralleled by an increase in CVD risk.[36,51]

Currently, it is unknown what determines visceral/subcutaneous fat distribution, but exercise training or caloric restriction preferentially lead to visceral AT loss.[45] Defects in lipid droplet formation are also critical in favouring visceral (rather than subcutaneous) adiposity.[56] Clinical observations imply that the inability to store fat in subcutaneous AT depot increases the propensity for visceral fat storage.[57] Nevertheless, expansion of the deep (rather than the superficial) abdominal subcutaneous AT layer could adversely affect CVD risk, given its morphological and functional similarity to visceral AT.[58]

5.3 Ectopic adiposity

The biological significance of ectopic fat depots for cardiovascular physiology has only recently becoming apparent.[10,12,13] In the case of epicardial AT, clinical studies have consistently demonstrated a positive association of epicardial AT volume with coronary atherosclerosis and CVD risk.[59] Epicardial AT has a phenotype closer to that of visceral AT, with smaller adipocytes and lower insulin-induced glucose uptake compared to subcutaneous AT, and lower lipid storage and lipolytic capacity compared with other human fat depots.[60] EpAT expresses brown AT-signature genes,[61] and its transcriptome significantly differs from that of subcutaneous or visceral fat,[62] being altered in the presence of coronary atherosclerosis, and shifted towards a pro-inflammatory phenotype.[12] We have recently demonstrated[10,12] that epicardial AT is in bidirectional communication with the myocardium. Changes in myocardial redox state, e.g. an increase in NADPH oxidase activity and increased 4-hydroxynonenal formation, trigger local rescue responses in the adjacent epicardial AT and increase PPARγ and adiponectin expression in a close feedback loop to combat increased myocardial oxidative stress.[12] Secreted adipokines also regulate cardiac fibrosis, cardiomyocyte electrophysiological properties, calcium cycling, and electromechanical coupling.[12,63] Therefore, epicardial AT secretome affects cardiac biology, whilst 'inside-to-outside' signalling from the heart (e.g. 4-hydroxynonenal, cardiac natriuretic peptide and possibly others too) also modifies epicardial AT biology.[10,12,13]

Thus, it is not clarified whether changes in epicardial AT biology precede or follow CVD development or how epicardial fat expansion is exactly regulated. Epicardial adipogenesis can interestingly occur as a response to cardiac disease too. Mesenchymal stem cells of epicardium undergo an adipocyte transformation in response to adipogenic stimuli released from cardiomyocytes.[63,64] For example in murine models of myocardial injury, epicardial progenitor derived cells differentiate to adipocytes around the necrotic infarcted area.[63,64] Similarly peri-atrial AT accumulation in AF has been suggested to be the result of pro-adipogenic factors released by dysfunctional atrial myocytes.[64]

Next to epicardial AT, recent studies from our group and others have highlighted the important role of perivascular AT (PVAT) for vascular health.[11,13,48] Vascular injury induces rapid phenotypic changes in murine PVAT.[65] Nonetheless the study of PVAT in mice has limitations and any findings may not be directly translatable to humans, since PVAT in mice (in contrast to humans) is brown AT.[66] Whilst murine PVAT is resistant to inflammation by high-fat feeding,[66] human obesity is associated with PVAT inflammation[67,68] and pro-contractile effects on small arteries function,[68] which are reversed by bariatric surgery.[68] According to recent translational evidence[11,13] human PVAT hosts defensive mechanisms which may be important for the prevention of atherosclerosis development. Increased vascular NADPH oxidase-derived superoxide and lipid peroxidation trigger the activation of protective pathways in PVAT, acting in a close-feedback loop to attenuate Nox2 activity and increase eNOS coupling.[11,13] Even though PVAT minimally contributes to the overall body fat mass, the study of PVAT phenotype in human obesity[66,67] and the identification of vaso-protective defence systems hosted in human PVAT[11,13] have contributed to the better understanding of obesity-related vascular disease.

Other types of ectopic adiposity seem to be biologically important too. Fatty liver content is independently associated with systemic insulin resistance and visceral fat accumulation, even though it is debatable

whether it is a cause or marker of disease.[38] Bone marrow AT content is involved in bone mineral density and skeletal health, and the study of lipodystrophy models has also shown that marrow AT is important for systemic metabolism too.[37] The effect of marrow AT content on CVD risk may be negligible compared to other body fat depots, but its role may be important in regulating body metabolism during cachexia states.[37]

5.4 Hypertrophic and hyperplastic AT expansion

The differential effects of fat depots on cardiovascular risk[35,36] are currently appreciated to be caused not only by the distinct properties of visceral vs. subcutaneous adipocytes but also by the type of expansion each AT depot undergoes during periods of positive energy balance. Reduced adipogenic potential of human subcutaneous adipocytes may shift energy storage towards visceral AT and underlie the mechanisms of obesity-related insulin resistance.[56] In mice prolonged high-fat diet leads to AT expansion from week 1,[54,69] but whilst visceral AT expands both by hyperplasia (increase in cell numbers via preadipocyte differentiation) and hypertrophy (increase in cell size by lipid droplet expansion), subcutaneous AT has low hyperplastic potential and is mainly hypertrophied.[54] Conversely, studies looking into the in vitro differentiation patterns of human adipocytes have observed a higher differentiation and adipogenesis potential of subcutaneous adipocyte precursors, suggesting that subcutaneous AT responds to positive energy balance with hyperplasia.[70] Thus, in vitro and animal studies' findings should be carefully translated to human AT.

It has been traditionally believed that AT hyperplasia represents a healthier mechanism of expansion by preventing adipocyte hypoxia, adverse ECM dynamics, and pro-inflammatory alterations.[71] However, the distinction between 'healthy' (hyperplastic) and 'unhealthy' (hypertrophic) obesity may be simplistic, particularly when applied to diverse AT depots, characterized by distinct baseline adipocyte phenotype, adipocyte precursors, and/or adipogenesis mechanisms.[56] Other mechanisms of hypertrophy, such as those regulating adipocyte lipid metabolism, are crucial for healthy AT expansion. Lipid droplet formation and expansion protects vital organs (e.g. heart, muscles, liver) from ectopic lipid deposition.[71] In pre-clinical models, facilitation of fatty acid uptake and lipid droplet formation is beneficial against the metabolic abnormalities of high caloric intake, and preserves systemic insulin sensitivity despite massive obesity.[72,73] Proteins involved in the process of fatty acid uptake (e.g. fatty acid transport protein or caveolin-1) and storage (e.g. perilipin) are critical determinants of effective lipid droplet expansion and AT health.[56]

5.5 Matrix plasticity, adipose angiogenesis, and tissue hypoxia

Further to the effective formation of lipid droplets and adipocyte hypertrophy, 'healthy' expansion of adipocytes is highly dependent on the plasticity of ECM.[69,74] During periods of high energy intake, expanding adipocytes quickly reach the local limit of tissue oxygen diffusion and become hypoxic. Acute hypoxia of adipocytes, as a result of hypertrophy, is a physiologic stimulus for collagen breakdown, ECM remodelling and VEGF-mediated angiogenesis to allow for further 'unstressful' AT expansion.[69] Therefore, stimulation of VEGF-A-mediated-angiogenesis early in periods of high-fat feeding has beneficial effects on the expanding AT.[74] On the opposite, chronic high-fat feeding and obesity-related insulin resistance are associated with chronic AT hypoxia, inappropriate angiogenesis and a fibrotic, inelastic ECM, which limits further expansion of adipocytes, and results in their dysfunction.[69,75] In this context of pre-existing adipocyte dysfunction, inhibition of angiogenesis may be beneficial by reducing AT insulin resistance and inflammation. In animal models with weakened ECM, e.g. collagen VI-null mice, AT expands uninhibited, and reduced AT macrophage infiltration with systemic improvements in metabolic homeostasis are observed even with high fat diet.[75] Thus, ECM dynamics and its plasticity determine the capacity of AT to expand whilst retaining a benign phenotype despite increased fat mass.[75]

5.6 AT inflammation: the role of infiltrating macrophages

AT inflammation and related adipocyte dysfunction can be both the cause and the consequence of CVD.[10,65] In humans, there are distinct differences among AT depots in the degree of macrophage infiltration and M1 polarization status.[10] The '*portal theory*' of obesity supports that visceral AT inflammation in abdominal obesity is the culprit event for induction of systemic insulin resistance and low-grade inflammation.[58] The pathogenesis of obesity-related inflammation is though now better understood. AT expansion and hypertrophy, limited by the plasticity of ECM can result in hypoxic adipocytes and initiation of a vicious cycle of local pro-inflammatory activation, autocrine/paracrine effects on adipocytes favoring chemokine production and triggering of further immune cell infiltration in AT.[56] Adipocyte death and hypoxia, chemotactic messengers released by adipocytes and increased free-fatty acid flux can all feed-forward crown-structure formation of activated macrophages around adipocytes resulting in global AT inflammation.[76] Adipocyte secretome is also shifted towards a pro-inflammatory phenotype, contributing to adverse systemic metabolic effects, insulin resistance and endothelial dysfunction in obesity.[56] Human obesity is associated with increased infiltration of PVAT of small arteries by macrophages.[68] Weight reduction and exercise have favourable effects on visceral and subcutaneous AT biology, reducing pro-inflammatory cytokine production and inflammatory cell infiltration in severely obese subjects.[68,77] Similarly, bariatric surgery attenuates PVAT infiltration by macrophages and benefits small arteries function.[68]

A causative link between obesity-related AT inflammation and atherosclerosis is currently well-accepted but vascular disease can also lead to AT inflammation.[65,78] In experimental models, vascular wire-injury induces potent TNFα-dependent pro-inflammatory responses in surrounding PVAT and accumulation of F4/80^{+} macrophages.[65] In humans, PVAT close to atherosclerotic human aortas is highly infiltrated by macrophages.[78] Such evidence suggests that 'inside-to-outside' signals from the vascular wall to surrounding tissues can result in local PVAT inflammation and altered adipokine production.[65,78] PVAT inflammation as a consequence of vascular dysfunction can feed-forward atherogenesis by effects on vascular smooth muscle cells hyperplasia and plaque formation.[65,78]

5.7 AT browning

Human fat is mainly white AT, but within it islets of brown adipocytes can be found too. In contrast to white, brown adipocytes derive from different adipocyte precursors and have a completely different gene expression signature, closer to that of myocytes.[79] White adipocytes can be transformed to beige adipocytes (an intermediate phenotype between the white and brown ones) upon appropriate stimulation.[80] Beige adipocytes can be also derived from *de novo* beige adipogenesis from precursor cells of white subcutaneous AT.[54] An overview of white, brown, and beige adipocyte lineages is provided in *Figures 2* and *3*.

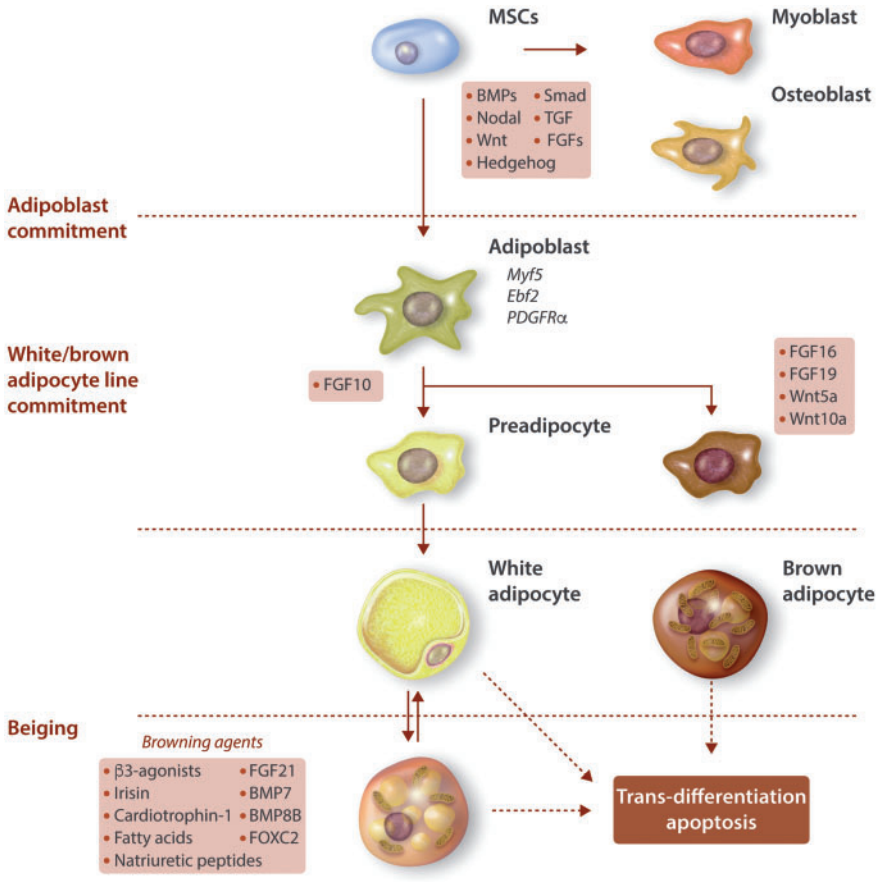

Figure 2 Human adipogenesis. Adipose tissue originates from mesenchymal stem cells (MSCs) or bone marrow progenitor cells that commit to the adipoblast lineage under the influence of adipogenic factors. The adipoblast then gives rise to the white or brown adipocyte preadipocytes. Next to de novo brown adipogenesis, white adipocytes can undergo a 'beiging' process under the influence of browning agents and be interconverted to beige adipocytes. Regulators of adipogenesis are presented in boxes.

AT browning has recently drawn much attention for its therapeutic potential against obesity, diabetes, and obesity-related CVD. Browning of AT could counteract the perils of excessive AT lipolysis to adipocytes *per se* (e.g. by consuming excess free-fatty acid release to generate energy).[81] Implantation of human beige adipocytes improves metabolic homeostasis in mice[53] and increased mass of beige AT could be directly related to a healthy adiposity. Nevertheless, the study of brown AT in animal models (or even humans) is challenging, since under thermoneutral conditions, murine brown AT is indistinguishable from beige/white AT.[82] AT browning can be achieved by diet or exercise, and thus the '*fat but fit*' hypothesis could be partially explained by the beneficial effects on adipokine expression and systemic metabolic status induced by exercise-mediated AT browning.[83] Secreted peptides from muscles such as irisin,[84] cardiac natriuretic peptides[85] cardiotrophin-1,[81] or signals produced locally by adipocytes e.g. FOXC2, FGF21, BMP7, and BMP8B[86] have been also identified as browning agents. Whilst the exact mechanisms of AT browning in distinct fat depots are not fully clarified, it is well accepted that AT browning/beiging process leads to beneficial local and systemic metabolic effects. AT phenotyping for beige/brown signature genes or assessment of its browning potential could help identify a metabolically benign AT phenotype.[87]

6. Assessment of obesity-related cardiovascular risk beyond BMI: established concepts and future perspectives

Taken together, recent clinical and translational evidence has shed light on the complex relationship between obesity and CVD. In primary prevention setting, the adverse effects of obesity on cardiometabolic health are indisputable, and ample evidence suggests a positive relationship of most obesity indices (anthropometric[26] or imaging[36]) with CVD and mortality risk. Nevertheless, in patients with established CVD, the obesity-mortality relationship is puzzling.[2] It is now understood that the 'obesity paradox' is BMI-related and solved when other adiposity markers are introduced, whose use should be encouraged for screening purposes.[7] Still, the assessment of obesity-related risk is perplexed by certain pertinent observations.

First, the limitations of anthropometric indices to classify obesity should be acknowledged. Anthropometric indices of obesity are simple and easy to measure and thus constitute ideal screening tools for the diagnosis of obesity. A major limitation though of anthropometric indices

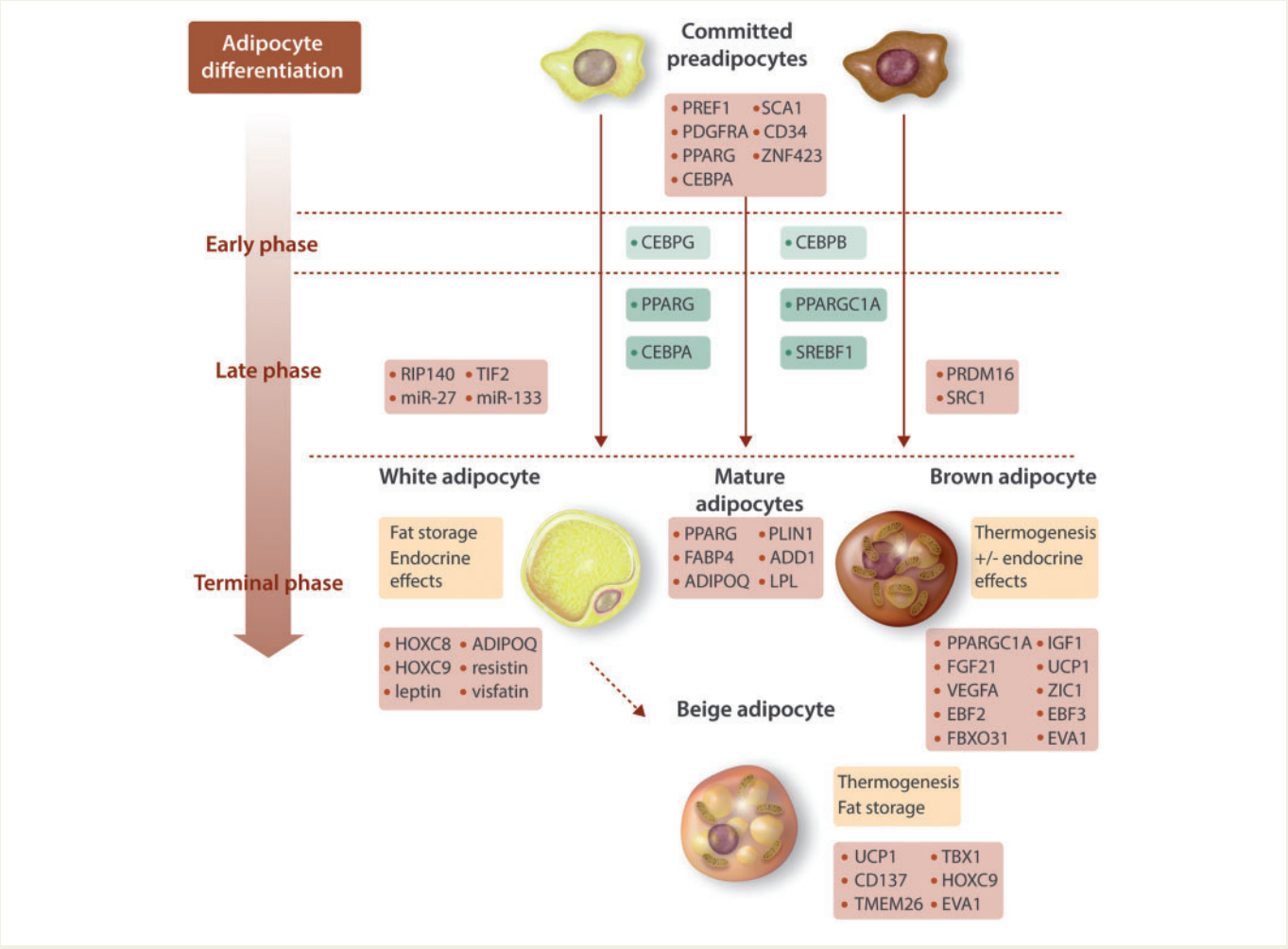

Figure 3 Adipocyte differentiation. Preadipocytes are differentiated to white or brown mature adipocytes respectively via the action of common differentiation factors or white/brown ones. Adipocyte differentiation phase starts by a decrease in Pref1 expression and upregulation of adipocyte differentiation markers (early and late phases). Terminally differentiated, mature adipocytes are characterized by expression of lipogenic genes, lipid droplet formation and the expression of white or brown/beige signature markers. Adipocyte differentiation factors are presented in boxes; cell signature expression markers are presented in italics.

is that universal cut-off values (albeit convenient in clinical practice) may not be valid for all ethnic groups for the classification of obesity (e.g. in Asian populations[88]). The use of additional obesity indices beyond BMI (e.g. *Table 2*) should be encouraged to diagnose obesity. Imaging biomarkers of obesity could also offer additional help and/or prognostic information, but issues related to their cost-effectiveness and/or cut-off values need to be answered first.[89]

Secondly, the identification of a low-risk obese group has been based to date on the MHO clinical criteria, i.e. BMI or BF% criteria and assessment for metabolic abnormalities. Based on the MHO concept the absence of metabolic syndrome criteria or high levels of CRF identifies a 'healthy' or 'low-risk' obesity profile. This is expected given the beneficial effects of exercise training on total body health and obesity-related metabolic disturbances and AT phenotype. In humans, exercise intervention programs induce significant percent reductions in visceral AT mass (even in the absence of concomitant weight loss).[45] In animal models, transplantation of exercise-trained subcutaneous AT improves overall metabolic health.[90] Exercise-training program reduces adipocyte size and lipid content of both visceral and subcutaneous fat depots, induces Prdm16-mediated beiging of adipocytes and UCP1 expression,[83] promotes AT vascularization, upregulates adiponectin as well as the expression of >3000 genes involved in adipocyte metabolism, mitochondrial biogenesis, oxidative stress, and signaling.[83] Therefore, the link between MHO and benign AT features at molecular level could be dependent on exercise and fitness effects, but other causes such as genetics, nutritional habits, environmental factors, and AT features[45] could also play a role in the healthy obesity phenotype. Thus, further research in this field is vital to explore the value of additional biomarkers in diagnosing MHO and/or expanding its definition.

Thirdly, investigation into the obesity-related mortality risk in patients with established CVD is much more complex, given the translational evidence suggesting two-way interactions between AT and the cardiovascular system.[10,12,13,33,67,78] The deregulation of adipokines secreted by human AT in obesity participates in obesity-related vascular disease. Nonetheless, reverse signalling from human vessels or the heart to AT can also drive pro-inflammatory changes in AT genomic and secretomic

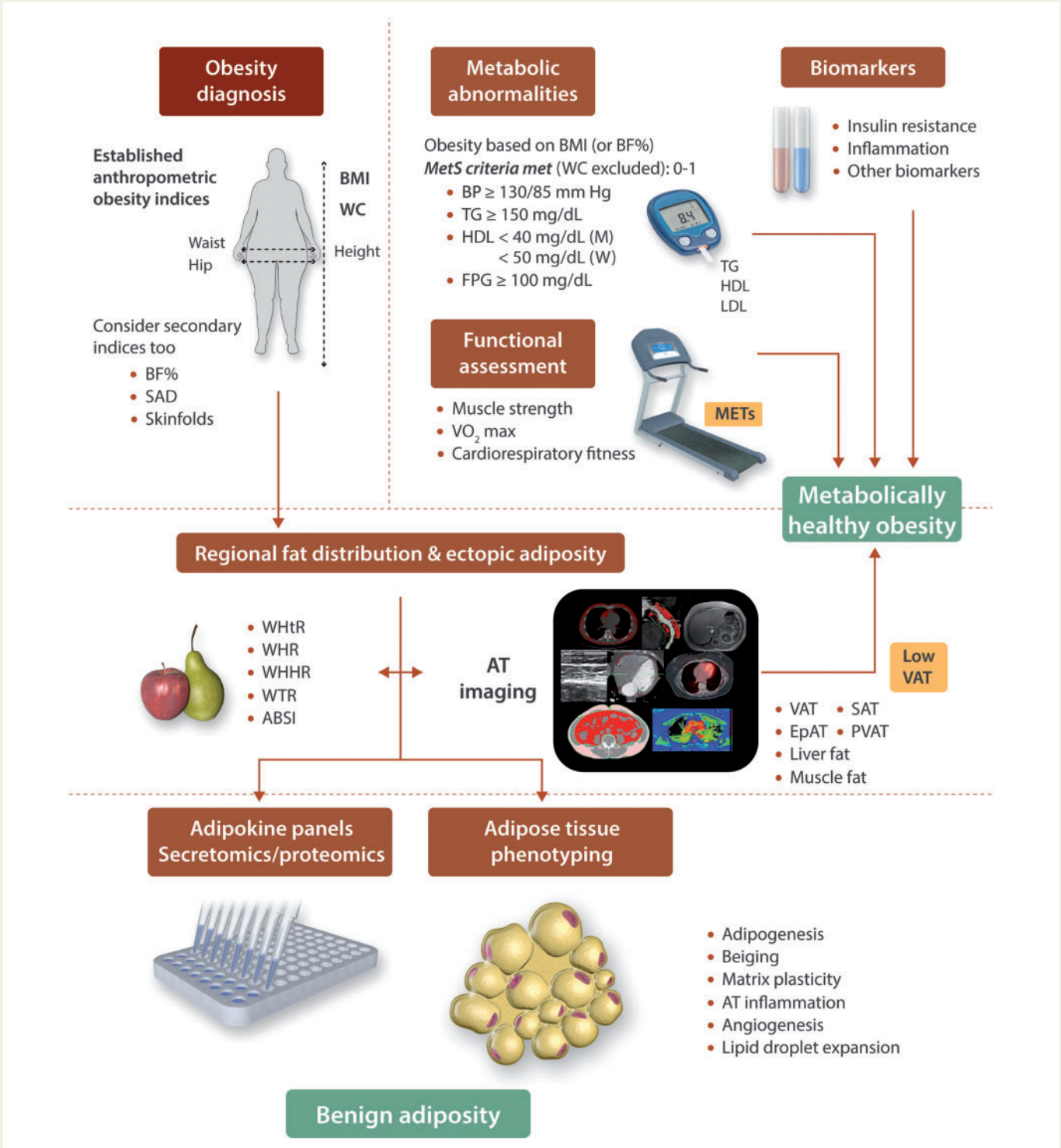

Figure 4 A multilevel approach to assess the obesity-related cardiovascular disease risk. *Obesity diagnosis* should be based on the use of anthropometric indices with established cut-off values, such as body mass index (BMI) or waist circumference (WC), but other obesity indices can be considered too. Further assessment for the presence of *metabolic abnormalities* (i.e. metabolic syndrome, MetS) and/or *cardiorespiratory fitness* could help identify the metabolically healthy (but) obese (MHO) individuals, associated with lower cardiovascular disease risk. Secondary indices such as *plasma biomarkers* of insulin resistance, systemic low-grade inflammation or others could also contribute to the risk stratification of obese subjects. Assessment of *regional fat distribution* by use of additional anthropometric measurements or non-invasive imaging of body fat depots, e.g. visceral abdominal (VAT), subcutaneous (SAT), perivascular (PVAT), as well as *ectopic adiposity* (e.g. epicardial/pericardial, liver and intramuscular fat) could provide additional prognostic information, independently of BMI. The ultimate goal of identifying the metabolically benign adipose tissue is expected to be reached by taking into account adipose tissue secretomic profile and aspects of its phenotype, such as its adipogenic/angiogenesis capacity, matrix plasticity, macrophage infiltration, browning potential, and mechanisms of lipid droplet expansion. ABSI, a body shape index; BF%, body fat%; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; MET, metabolic equivalent; VO_2max, maximal oxygen consumption; TG, triglycerides; WHtR, waist to height ratio; WHR, waist to hip ratio; WHHR, waist-to-hip to height ratio.

profile in disease states.[11–13,65] Thus an 'unhealthy' AT phenotype in such patients may not be the cause, but rather the result of CVD. For example in coronary patients, the expansion of epicardial and perivascular AT depots[63] and local AT infiltration by macrophages could be the result of advanced vascular or cardiac disease.[33] Currently, the relative biological importance of perivascular/epicardial AT vs. visceral/subcutaneous adiposity for cardiovascular health is not known and conclusions on cause and effect relationships between AT features and CVD cannot be safely drawn.

Finally, complex information on AT biology cannot be easily incorporated in clinical studies, which have primarily used anthropometric indices or volumetric data on human fat depots to explore the obesity-related risk beyond BMI.[2,59,89] Other important biological aspects, e.g. AT inflammation or AT browning, can be studied invasively by gene expression profiling and immunohistochemistry of AT biopsies. Non-invasive imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography/computerized tomography (^{18F}FDG PET/CT) imaging could be useful in assessing AT metabolic activity (as a surrogate marker of AT inflammation and/or activation of brown/beige adipocytes), but its widespread application in clinical studies is limited by the radiation exposure.[89] PVAT imaging could also provide useful information on AT biology and obesity-related vascular inflammation and atherosclerosis risk, but currently there are no available modalities to incorporate such information in useful clinical risk models.[89] Overall, in addition to strategies that promote a favourable adiposity profile, novel approaches for the characterization of AT, e.g. by use of molecular or imaging biomarkers, would be useful to assess human obesity-related CVD risk in primary or secondary prevention settings.

Based on current concepts about human adiposity, *Figure 4* provides an overview of how the obesity-related cardiovascular risk should be approached.

7. Concluding remarks

In conclusion, clinical observations and translational evidence suggests that a metabolically benign AT phenotype exists, which can explain the paradoxically low CVD risk of certain obese individuals. Thus adiposity is not necessarily unhealthy, but it depends on aspects such as regional fat distribution, the adaptations of AT to excess caloric intake and the type of fat expansion. The role of fitness seems to underlie MHO, but certain AT molecular features, are also intrinsically linked with a healthy AT, allowing for excess adiposity without adipocyte dysfunction. Future research on human AT biology is expected to provide insight into ways to promote healthy fat storage and prevent adipocyte dysfunction in obesity and help develop novel molecular or imaging biomarkers for the characterization of AT quality next to its quantity in order to better assess the obesity-burden to the cardiovascular system.

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