Fat, yet fit.

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Stand first

Susceptibility to impaired metabolic health in relation to obesity is not necessarily mediated by overall fatness, but is largely dependent on distribution of body fat and the ability to sufficiently expand adipose tissue. A recent study published in *Diabetes*, provides genetic evidence to support the concept of a 'metabolically healthy obese' phenotype.

Main text

Although obesity is an important determinant of metabolic health, type 2 diabetes mellitus (T2DM), hypertension and cardiovascular disease risk, not all overweight individuals encounter these health problems. In terms of a mechanism linking obesity with metabolic complications of fatness, it would seem intuitive that a very effective fat storage in adipose tissue would sequester potential detrimental lipids from ectopic fat storage or reduce lipotoxicity in cells or tissues lacking dedicated fat storage capacity. A mechanistic framework supporting this was proposed by Eliot Danforth who stated that 'type II diabetes is the result of inability of adipose organ to expand to accommodate excess calories' [1]. The concept of 'adipose tissue expandability' has subsequently been extended and refined by Vidal-Puig and co-workers [2]. The concept is not specific to individuals with obesity, but is also observed in individuals with normal BMI, in whom the insulin resistant phenotype is seen in the context of insufficient fat storage capacity due to a dysfunctional fat tissue. The extreme example of this situation is found in people with severe restrictions in adipose tissue fat storage capacity such as complete or partial lipodystrophy. By contrast, if individuals with obesity have the inherent capacity to sufficiently expand their adipose depots, they will be protected against the ill-effects of fatness, and have a normal metabolic profile despite considerable enlargement of their adipose tissue depots. This profile is often referred to as the 'metabolically healthy obese (MHO)' phenotype.

In 2014, Yaghootkar and colleagues made a paradoxical and important observation while selecting a cluster of 11 common genetic variants relating to fasting insulin levels (a marker of fasting insulin resistance) from Meta-Analysis of Glucose and Insulin Consortium (MAGIC) genome-wide association study (GWAS), that were associated with T2DM, abdominal obesity, dyslipidaemia or markers of cardiovascular disease [3], but with a lower than expected body mass index (BMI). As this constellation resembled a lipodystrophy-like phenotype, the data suggested that milder forms of this otherwise very rare and severe condition are rather common. The relationship between T2DM risk and adiposity has now been further investigated using the 11 common genetic variants of insulin resistance in addition to 69 variants associated with increased BMI from another GWAS [4]. By using the complementary allele of the insulin resistance gene variants, these alleles were renamed as 'favourable adiposity alleles', that is, primarily associated with increased adiposity (higher BMI), yet

coupled with a reduced frequency of metabolic complications of obesity. In their most recent study [5], Yaghootkar and colleagues explored these associations further in 164,609 individuals participating in the UK Biobank and confirmed that the carriers of the favourable adiposity alleles indeed have a higher BMI and body fat percentage but, paradoxically, lower risk of T2D, hypertension and heart disease than noncarriers of these favourable adiposity alleles. Each additional favourable adiposity allele' was associated with an odds ratio (OR) of 0.943 [95% CI (0.924, 0.963); p=2E-8] of T2D. This gives important confirmation of the previous observations and robust evidence that the MHO phenotype has some element of genetic underpinning. However, it turns out that the observed effect (fat-fit phenotype) was driven by 7 of the 11 'favourable adiposity alleles', whereas 4 gene variants did not contribute, or had the opposite effect. A very similar effect on diabetes protection was observed using the larger number (n=69) of unselected GWAS variants for obesity in general. Carriers of these variant had an equally strong effect on the fat-fit phenotype with each obesity allele associated with a 0.885 OR [95% CI (0.813, 0.965); p=0.005] for T2D. This finding rocks the concept of 'favourable adiposity alleles' conveying the effect, as it appears that the effect is driven by the genetic risk for obesity as such.

So, what could explain the paradoxical associations observed by Yaghootkar and colleagues [5]? In their report, the investigators explore one possible mechanism: fat distribution. Beyond BMI, the favourable adiposity alleles were associated with increased hip circumference (HC) and reduced waist-hip ratio (WHR) in women, which is consistent with a change towards a gynoid type of body fat distribution that is co-linear with the BMI. An effect on fat distribution in this direction could possibly explain some of the T2DM protection [6], but the authors do not formally test this hypothesis. The situation was somewhat different in men, in whom the increased weight driven by the favourable adiposity genes seemed to be distributed much more equally over the entire body. Both waist circumference and hip circumference increased, albeit waist circumference to a rather slightly greater extent. Although Yaghootkar and colleagues conclude that this phenotype resembles a change towards the archetypical android fat distribution, it could equally be interpreted that men with this genetic predisposition tend to acquire a more evenly distributed fat mass, and possibly of largely subcutaneous nature. Again, this type of fat distribution is probably less harmful in terms of T2DM risk than, for example, visceral fat accumulation.

We propose an additional explanation for the paradoxical finding that common genetic variants predisposing individuals to adiposity can exert a T2DM-protective effect. The current observation was made in adult individuals and is cross-sectional by nature of the cohort. Consequently, the effect obesity gene variants might have had earlier in life is ignored. In fact, GWAS obesity gene variants affect adiposity and/or BMI from birth and continue to do so during childhood

and development [7,8]. Carriers of these variants have higher BMI than noncarriers throughout early growth and development, the time when adipocyte numbers are established [9], as well as when plasticity in the development of the endocrine pancreas still exists. Conversely, when individuals without these priming events (that is, incipient childhood fatness) encounter a positive calorie balance during adulthood, adipose tissue and pancreatic ß-cells might have a restricted capacity for adaptation, and the individual would easily fall into the 'metabolically-unhealthy obese' phenotype. Individuals with this constitution have been postulated to have a low 'personal fat threshold' (Figure 1)[10]. The reduced risk of obesity complications observed in people carrying the favorable adiposity allele, or the general GWAS obesity gene variants is, of course, only relative to the comparator group. The lowest risk of T2DM will still be found in people who do not become overweight, probably irrespective of whether they carry favorable adiposity alleles or not.

However, the postulate that obesity gene variants impact on critical metabolic organ growth and development from an early age can only be tested in large scale longitudinal birth cohorts.

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Legend for figure

Figure 1 | Regulation of "metabolically healthy obese (MHO)" phenotype. Body fat distribution and weight gain are regulated by complex genetic and epigenetic mechanisms that are probably governed by unique sets of developmental genes with tissue-specific expression, operating even *in-utero*. This, together with the cues for energy balance, dictates the individual adiposity status throughout life. It is hypothesised that a chronically overweight child in face of sustained positive energy balance adapts the adipose tissue depots to sufficiently store excess fat, while in a non-obese child such priming of adipose tissue does not occur. Upon exposure to toxic environment of calorific excess in adulthood these two backgrounds will matter. Childhood priming (carrying the obesity genes) is likely to serve as a protection against complications of obesity, such as type 2 diabetes. In the adult without the priming, there will be a premature crossing of the individual fat threshold for adipose tissue expandability.