Treatment strategies for chronic diseases that do not tackle excess adiposity are promoting multimorbidity

Research into obesity and action to establish effective weight management should receive funding to match the search for and use of novel therapeutics for secondary chronic diseases

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Few people now reach old age without taking multiple drugs, attending multiple clinics, often undergoing secondary or tertiary investigations. Numerous chronic conditions are to some extent caused by excess adiposity. Yet, weight management is rarely discussed or attempted in many patients. Furthermore, multiple symptoms usually attributed to aging – e.g. musculoskeletal pains, fatigue, breathlessness – which create considerable healthcare demands – also could be attributed to the accumulation of body fat over time.[1,2] For many of the latter symptoms, and psychological diseases such as depression which are more frequent amongst the overweight,[3] there exist potentially multi-directional, causal relationships which generate a vicious cycle of clinical and social deterioration. Insufficient research has explored the impacts of effective weight management on these clinically demanding, age/weight-mediated, symptoms.

How did we reach this point? Paradoxically, one reason is the documented success of modern medicine in helping to reduce premature mortality. Cardiovascular deaths are no longer the most common cause of death in high and some upper middle income countries,[4] or among individuals with conditions like type 2 diabetes.[5] That fall in premature mortality has been mediated firstly by reduced smoking rates, and secondly by reduced population cholesterol and blood pressure levels.[6] Reductions in salt, saturated and trans-fats in foods have also contributed. In addition, there have been widespread improvements in acute clinical care and healthcare system performance,[6–8] including increased cholesterol-lowering and antihypertensive drug use, as treatment goals have intensified through adoption of guidelines. Analysis of data from the US found that 44% of decline in coronary heart disease mortality between 1980 and 2000 was attributable to reductions in major risk factors (including improved diet quality) and approximately 47% to evidence-based medical therapies.[6]

Those pharmacologic treatments have improved outcomes for many chronic diseases, leading to fewer premature deaths and longer survival. Rheumatoid arthritis (RA) provides a notable exemplar. RA is a common inflammatory disease which reduces life expectancy, in part by promoting premature cardiovascular disease. Early intervention and the development of advanced immune targeted therapeutics have revolutionised care, allowing many patients to achieve low disease activity or remission, thereby minimising cachectic inflammatory processes, and improving survival.[9] Survival after the onset of heart failure has improved with new drugs and procedures, from less than 5 to over 10 years.[10] With type 2 diabetes, earlier diagnosis, closer adherence to evidence-based guidelines, safer glucose-lowering

medications (some with cardiovascular benefits), and better cardiovascular risk management, have increased life expectancy.[11] After acute coronary events and strokes, multifactorial treatments, procedures, secondary prevention, and rehabilitation have all improved survival. Many major cancers are now considered treatable conditions, with lengthy remissions possible. These are all 'good news stories', and many chronic diseases are no longer feared as before.

However, this ostensibly better position may have down-sides. Specifically, celebrating success in secondary prevention of chronic diseases can neglect the fact that this success is only partial: they remain disabling diseases and are not yet cured. It has also tended to divert thinking and necessary effort from tackling their modifiable 'upstream' root-causes – specifically in this context, the *disease-process of excess body fat accumulation*, i.e., 'obesity'.[12,13] Obesity is not simply defined as a state of high BMI. Its disease-process may manifest as increased total body fat and higher BMI, but also as ectopic fat deposition in vital organs with apparently normal BMI. BMI is a relatively crude indicator of body fat: it fails to distinguish fat and lean tissue. A larger waist circumference better reflects the health risks related to intra-abdominal ectopic fat accumulation,[14] and better estimates of body fat and muscle mass can be made, using validated equations which employ the same simple data collected in routine health surveys.[15,16]

With this broader definition of obesity as a disease-process, it is increasingly recognised as a causal risk factor for many chronic conditions. Recent elegant epidemiological studies and genetic analyses tracking the wide impact on outcomes of adiposity genes and lifelong higher BMI have now linked excess adiposity causally to multiple conditions. The list includes increased total mortality[17] (from studies mostly before major increases in preventive efforts), fourteen cardiovascular diagnoses (including MI, stroke, atrial fibrillation, hypertension, and heart failure),[18] type 2 diabetes, fatty liver disease, chronic kidney disease (CKD),[19] osteoarthritis, rheumatoid arthritis, psoriasis, gastrointestinal disorders,[20–22] plus exacerbations of COPD[23] and multiple cancers.[24] Causality is further demonstrated by robust evidence that type 2 diabetes can be both prevented and reversed into remission with weight loss.[25] Emerging evidence that many other chronic conditions can be improved or prevented by weight loss[26–30] further supports the notion of causal inferences.

Thus, improving treatments and extending life expectancies in many chronic diseases, which is of course welcome, has unmasked a compelling need to tackle a significant "upstream" causal contributor to many conditions, namely excess adiposity. Put simply, when patients are treated for one such condition, they now live longer but if this promotes greater exposure to untreated, excess adiposity there may be paradoxical acceleration of the development of other conditions (**Figure 1**). This potentially uncomfortable recognition is strongly supported by the experiences of many healthcare professionals across numerous specialities, and by recent findings across three different western population cohorts.[31] Compared with healthy weight, the confounder-adjusted hazard ratio for BMI >30 was 2·8 for developing at least one obesity-related disease, 5·2 for two diseases, and 12·4 for complex multimorbidity.[31] These data make sense, as excess adiposity has multiple adverse impacts across metabolic (e.g., lipids, dysglycaemia, ectopic liver fat), physical (e.g., joint stress, inactivity, GI reflux, sleep apnoea), haemodynamic (e.g., blood pressure, volume excess), inflammatory signals, and other pathways which mediate disease occurrence and aggravation.

Taken together, these findings should compel us to give more emphasis to weight reduction (or prevention of further weight gain) when treating our patients, irrespective of which chronic disease they present with. Otherwise, a perfect 'storm' arises. If patients with, for example, RA or heart failure receive earlier and better-targeted treatments, fewer experience inflammation-driven or cardiac cachexia-driven unintentional weight loss and fewer die prematurely from that disease. Instead, their underlying excess adiposity progresses with proportionally greater intra-abdominal and ectopic fat deposition over time, possibly even accelerating after successful disease treatment.[20,32] (**Figure 1**). This in turn, enhances the likelihood of development of additional diseases and de facto creates multi-morbidity (defined as two or more chronic conditions) which in turn will demand multiple treatments. Put simply, people are living longer with diabetes, other cardiovascular conditions, and many cancers, as examples, leading to greater overall aggregated exposure to excess adiposity, and so increasing development of adiposity-related comorbidities into older ages.

We have been slow to interpret epidemiological evidence properly. Many datasets that assess possible causal associations are 30-40 years old or more. Over that time, adiposity (and conventional BMI>30/obesity) levels have increased, at younger ages, whereas other risk factors (notably smoking) have lessened. Thus, while excess adiposity has become a progressively more important risk factor, this may not be apparent in some standard

epidemiological studies. Limiting survey reporting to BMI is employing a weak indicator of body fat, and has likely concealed more a critical role of intraabdominal and ectopic adiposity. It is worth reflecting that, the shift in human phenotype over the past 40-50 years, with average weight gain of more than 10 kg across whole western populations[33] means that very few people now have a BMI within the 'normal' range beyond the age of 60.[34] Most people who remain free from serious illness now gain weight, so the rather small BMI <25kg/m^2 category (under 15% by age 65[34]) now probably contains a significant proportion who have failed to gain weight, or lost weight, through subclinical or ongoing illnesses which reduce survival. Thus although the greatest life-expectancy is now found at a BMI a little above 25kg/m^2,[35] optimal BMI is probably still about 18·5-22kg/m^2, provided that is not the result of illness and unintentional weight loss. This notion is strongly supported by the Global BMI meta-analysis which found a BMI nadir at 20 to 21kg/m^2 consistent with lowest mortality risk in the youngest group (among whom unintentional weight loss is less frequent).[17]

How should the healthcare ecosystem respond? After effective tobacco control, efforts to prevent excess adiposity now appear to be the most important priority for public health. Given near 50% of the US adult population up to age of 35 may be living with BMI>30kg/m^2 by 2030,[36] representative of rising obesity levels worldwide, health services alone will never solve the obesity epidemic. Rather, health policy makers have critical roles to influence and deliver wider policies that would reverse the obesogenic environments which are worsening in nearly all countries. These might include changing the physical environment by, for example, making walking to work easier or by building safe cycles lanes as in some European countries. The latter changes are critical as physical inactivity levels are rising among young adults.[37] However, even if radical governmental-driven policy changes in the food industry or physical environments (incurring huge infrastructure costs) could reverse rising adult adiposity changes are unlikely to happen quickly. Moreover, this is most problematic among the more socially deprived where extreme obesity levels are greatest, but for whose social strata, policy induced change is most challenging. Perhaps unsurprisingly, no country has yet demonstrated effective action to reduce obesity. The 2022 Policy Brief by the International Diabetes Federation and the World Obesity Federation summarised the complex issues around prevention, noting that key determinants of obesity and diabetes originate outside the health sector, and can only be reduced through multisectoral approaches and innovation.[38] Well-intentioned health education has repeatedly proved ineffective,

particularly among young people, for whom a radical contemporary approach has been proposed.[39]

In our opinion, health authorities and funders would be wise to invest as much in researching and providing effective weight management, to tackle excess adiposity earlier, as is allocated for discovering and using new drugs which address non-obesity-related drivers of specific chronic diseases. Diet and lifestyle interventions place demands on the patient and have often been neglected on the grounds that many patients reject them or give up early and regain lost weight. Not every patient fully understands the risk and prognosis of conditions such as type 2 diabetes or is ready or able (in their environment or with current care given) to attempt the necessary changes to lose weight and maintain weight loss. Recent research is beginning to provide solutions. Educational nutrition sheets or other brief interventions cost little and have some effectiveness, even at the primary care level with potential population level impact.[40] Commercial weight loss providers can also help people lose considerable weight.[41] Basic education about diet and lifestyle and health at primary school level could have long-term impact. Simple, scientifically designed, food-based diet plans, using local and traditional ingredients, can be affordable for consumers who would like a reliable self-help strategy. Sadly, this may take time. Many traditional foods produced locally and cheaply, and consumed in large amounts prior to the obesity epidemic, have been steadily displaced in modern eating patterns by manufactured 'added-value' foods high in fat, sugar and salt, including 'snacks'. The reduced production and niche-marketing of foods such as vegetables and fruits has made them expensive in many countries.

A more intensive evidence-based service, whether face-to-face or remotely supported, can now reliably generate >10 kg weight loss for over 50% of people at 12 months, enough for most to achieve remission of type 2 diabetes.[25] Further evidence suggests such an intervention is likely cost-saving relative to standard care.[42] For those needing additional support, providing additional pharmacotherapy after low calorie diets[43] or bariatric surgical procedures can be life changing,[44] by improving risk factors, reducing micro and macrovascular events and enhancing quality of life, vitality and general well-being.[44] Bariatric surgery is not a simple cure, requiring lifelong dietary control and medical monitoring, and is an unattractive idea to many patients. It has however, provided strong evidence for long-term 'legacy' benefits from substantial sustained weight loss, even if the patient remains obese or overweight after surgery.

This evidence has opened the door for the emergence of newer GLP-1RA or combined GLP-1RA-GIP drugs, which with good dietary support can produce average weight losses of 15-25%,[45,46] approaching those achieved by surgery. These exciting medications are limited by cost and to a surprisingly minor extent by needing injections, but do offer the strong possibility that future comorbidities may be substantially delayed or prevented, at the same time as improving patients' quality of life and/or ability to work and contribute to society.

In summary, for the sake of future healthcare and society in general, it is time to turn to the high ground, to widen our medical focus from 'downstream' consequences, to also address one of the key 'upstream' drivers or disease-magnifiers, excess adiposity. This demands a paradigm shift, to recognise risk of promoting, or accelerating the development of, multi-morbidities arising from excess body fat accumulation. Better treatments for individual 'downstream' consequences of excess adiposity, that do not include weight management, result in greater lifetime exposure and burden attributable to excess adiposity, greater multimorbidity, resulting in greater patient suffering, and health care burden (**Figure 1**). Such exposure to higher adiposity levels is worsened at both ends of the life course, as weight levels are now rising faster in younger people.[36] Yet, with prioritised awareness and effective weight management, fewer will develop adiposity-mediated conditions or their complications, thus reducing multimorbidity and improving quality of life. The trick now is to research and upscale effective weight management strategies much earlier in the life-course of many chronic diseases, lest we risk worsening the already burgeoning multimorbidity crisis.

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NS conceived the idea for this article and wrote the first draft with MEJL. JJVM, IBM and VRA critically revised the manuscript for important intellectual content. All have approved the final submitted version.

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Figure Legend

Figure 1 *Multiple reasons for greater lifelong exposure to excess adiposity in many chronic diseases*

Exposure to excess adiposity has risen across the life course as compared to the weight patterns a few decades ago due to several factors, including A. An increase in obesity levels in general due to changes in food and activity environments, with evidence for faster rise in weight levels at younger ages, B. Reductions in smoking so that other factors – perhaps most commonly obesity – have become relatively more contributory to the development of many diseases, C. Better treatments of many chronic disease associated with inflammation and unintentional weight loss such as many cancers, autoimmune diseases and heart failure, so that such patients are now living much longer with their conditions and are evidentially heavier over the course of their condition (excess weight is a risk factor for many such conditions but has been overlooked before due to rapid weight loss incurred by these conditions), and D. Reductions in cardiovascular mortality in general and in many other conditions due to better primary and secondary prevention leading to people living longer with chronic conditions. The consequence of A to D is greater lifetime exposure to excess adiposity and a consequent rise in development of other conditions linked to excess adiposity. To reduce multimorbidity, therefore, the medical profession would do well to research targeting excess adiposity earlier in the course of multiple conditions. Such weight loss might improve the condition itself (whether rapidly or more slowly), improve quality of life, and should reduce development of future comorbidities, lessening pill burden and suffering, and crucially, improving quality of life. Of course, given the number of people now living with obesity, policies that help prevent obesity are also urgently needed but these require real political motivation and intervention over many years.