From adiposity to multisystem morbidity: the case for weight loss as disease modification

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Obesity (ie, excess adiposity) is a major driver of multisystem morbidity, spanning musculoskeletal (eg, osteoarthritis), metabolic (eg, type 2 diabetes), cardiovascular (eg, heart failure), mental health (eg, depression), respiratory (eg, obstructive sleep apnoea), and gastrointestinal and hepatic (eg, metabolic dysfunction-associated steatotic liver disease) disorders. However, the extent to which weight-loss interventions can prevent or modify these conditions varies considerably. In this Review, we synthesise evidence from epidemiological studies, genetic analyses (including Mendelian randomisation), observational weight-change studies, and randomised trials, using a triangulation framework to assess causal links between adiposity and common diseases. Although robust trial evidence supports weight loss as a disease-modifying strategy in some conditions, including but not limited to type 2 diabetes and heart failure with preserved ejection fraction, many other conditions, including musculoskeletal, respiratory, cardiovascular, and mental health disorders, remain under-investigated. Incretin-based therapies, in particular the glucagon-like peptide 1 receptor agonist semaglutide and the dual glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide, now achieve average weight losses of approximately 14–20% in people without diabetes and have generated the first large-scale randomised evidence of disease modification across several of these conditions. We highlight key gaps and propose priorities for future trials, including the need for studies across different disease stages, incorporation of mechanistic and mediation analyses, and evaluation of the impact on disease outcomes of varying magnitudes of weight loss with differing agents. Future research should also consider multimorbidity, individualised treatment targets, and long-term outcomes—including potential legacy effects. Addressing global access gaps and conducting trials in diverse populations will be essential to inform scalable and equitable obesity care.

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Introduction

Over the past four decades, obesity prevalence has risen in nearly all countries,[1,2] and in many high-income nations between one in six and one in three adults now live with obesity.[3] This rise, combined with widening health inequalities and longer life expectancy, means people are exposed to excess adiposity for more years than ever before. Such prolonged exposure accelerates ill health, contributing to multiple chronic conditions, poor mental health, pain, and fatigue.[4] As a result, many experience reduced quality of life, impaired ability to work until retirement, and earlier loss of independence. These patterns place growing pressure on health and social care systems and affect economic productivity.

We recently argued that obesity should be addressed more systematically across a wider range of conditions to prevent multimorbidity and improve quality of life.[4] Emerging dietary and pharmacological approaches that produce substantial weight loss offer renewed promise. Many people with cardiometabolic disease now benefit from structured weight management strategies, supported by trials in type 2 diabetes, heart failure with preserved ejection fraction (HFpEF), and metabolic dysfunction-associated steatotic liver disease (MASLD). Yet many other conditions could also improve or even be partly reversible with intentional weight loss.

However, the absence of robust weight-loss trials in many disease areas reduces clinicians' confidence and understanding of benefits, risks, and integration with standard care. Trials must show disease-modifying effects, assess safety, and evaluate impacts on quality of life, health-care use, and work productivity. Because obesity is an upstream driver of many conditions, early weight management could provide an efficient, wide-reaching intervention that benefits primary disease, co-existing conditions, and future risk. Early weight management could also reduce the need for higher doses of disease-modifying drugs with resultant patient and cost benefits.

We reviewed a range of chronic conditions (cardiovascular, musculoskeletal, respiratory, gastrointestinal, and depression), many of which have not been extensively studied in relation to obesity (figure; appendix pp 1–49). Although a comprehensive review of all obesity-linked conditions was not possible, the evidence presented should prompt clinicians to rethink treatment pathways and support more targeted clinical trials.

We use a triangulation framework, in which evidence from designs with different and largely unrelated sources of bias—observational epidemiology (susceptible to confounding and reverse causation), Mendelian randomisation (susceptible to pleiotropy but not to conventional confounding), observational studies of weight change, and randomised trials of intentional weight loss—is appraised side by side. Where these independent lines converge on the same direction and approximate magnitude of effect, causal inference is strengthened; where they diverge, or where randomised evidence is absent, we identify this as a priority for future trials. For each condition we therefore report all four evidence streams (tables 1, 2) rather than a single pooled estimate.

See Online for appendix

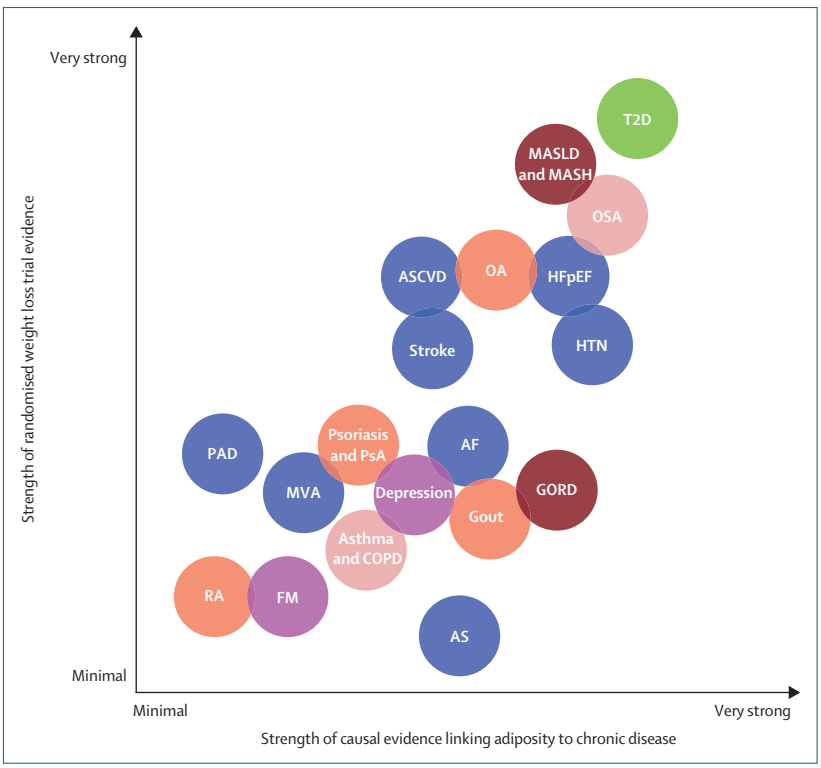

Figure: **Strength of causal evidence linking excess adiposity to chronic disease versus weight loss trial evidence**

Conditions are positioned approximately according to the strength and consistency of epidemiological and genetic evidence (x-axis) and the extent of RCT evidence showing disease-modifying benefit of intentional weight loss on a range of differing outcomes (y-axis). Colours group disease domains: green shows metabolic, blue shows cardiovascular, pink shows respiratory, orange shows musculoskeletal and skin, purple shows mental health and other, and red shows gastrointestinal and hepatic. T2D, OSA, MASLD and MASH, ASCVD, HFpEF, stroke, HTN, and OA occupy the upper and generally right-sided quadrant, reflecting both strong causal and interventional evidence. In contrast, AF, psoriasis, PsA, gout, GORD, depression, RA, asthma, COPD, PAD, and AS show established or moderate causal associations but remain under-represented in large RCTs, highlighting important translational gaps. FM and MVA show emerging but comparatively minimal trial evidence. GORD warrants particular care in trial design: incretin-based therapies delay gastric emptying and can increase reflux in the early months of treatment, so short trials risk showing net harm. Trials should therefore continue beyond 1 year, so that any early rise in symptoms can be weighed against the benefit of sustained weight loss. AF=atrial fibrillation. AS=aortic stenosis. ASCVD=atherosclerotic cardiovascular disease. COPD=chronic obstructive pulmonary disease. FM=fibromyalgia. GORD=gastro-oesophageal reflux disease. HFpEF=heart failure with preserved ejection fraction. HTN=hypertension. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. MVA=microvascular angina. OA=osteoarthritis. OSA=obstructive sleep apnoea. PAD=peripheral arterial disease. PsA=psoriatic arthritis. RA=rheumatoid arthritis. RCT=randomised controlled trial. T2D=type 2 diabetes.

Type 2 diabetes

Type 2 diabetes is the chronic disease most closely linked to excess adiposity, with multiple trials[5–7,43] influencing clinical practice (table 1). Epidemiologically, the higher BMI to incident type 2 diabetes link is robust, with hazard ratios exceeding 12 comparing obesity with healthy weight.[44] Additionally, strong genetic evidence supports the causal effects of adiposity on diabetes risk. Robust randomised trial evidence shows that intentional weight loss can lead to remission of type 2 diabetes,[5] with approximately 5% remission in the first 1–2 years for every 1% weight loss in those with recently diagnosed (<3 years) diabetes as reported in an analysis across three trials.[7] Remission by low-calorie diets has also been estimated to be cost-effective, such that remission by this method is now offered as a treatment option in several health-care systems, including the UK's National Health Service.[45] A 5-year follow-up of the diabetes remission trial (DiRECT), which focused on diet-driven weight loss, showed that although sustaining remission is difficult for many, serious adverse events were lower by approximately half in the intervention group versus controls, suggesting that reducing aggregated exposure to excess weight could reduce the risk of multiple adverse outcomes.[46]

Going forward, if new weight loss interventions can help sustain more than 10% weight loss over several years—whether low-calorie diet or pharmacological approaches combined with lifestyle—we have argued type 2 diabetes, when treated at or near diagnosis, could be reversed for many years.[47] Indeed, clinical trials of the GLP-1 receptor agonist semaglutide and of the dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide have shown significant reductions in bodyweight (in the order of ~14–20% in people without diabetes, with lesser weight losses of around 6–12% in people with diabetes) among individuals receiving these agents, with greater rates of reversion to normoglycaemia and substantially lower risk of progression to type 2 diabetes compared with placebo, not surprising given pre-diabetes is also a weight-driven phenomenon in most.[48,49] Indeed, in people with pre-diabetes, tirzepatide reduced the risk of incident type 2 diabetes by 93% compared with placebo over 3 years.[8] It should be noted, however, that weight loss reached by these agents might be lower in the real world and that more work is needed to address long-term adherence.

Hypertension

Notable improvements in blood pressure and dyslipidaemia have also been reported with incretin agents, with greater weight loss generally associated with greater risk factor changes.[49] There is, however, a need for more trials in people living with obesity and hypertension, including resistant hypertension, as rising obesity levels mean hypertension is now much more aligned with obesity than ever before. There is ample observational, genetic, and intervention evidence linking obesity to hypertension (table 1; appendix pp 1–17).[50–52] In a pooled analysis of 837 population-based studies, including 7·5 million participants, both general and abdominal adiposity were associated with higher blood pressure and hypertension prevalence across all eight world regions.[50] Mendelian randomisation studies support a causal contribution of higher BMI to blood pressure,[51] and a meta-analysis of bariatric surgery cohorts reported hypertension remission in a substantial proportion of patients.[52] Randomised data are consistent: in DiRECT, dietary weight loss allowed antihypertensive withdrawal in many participants without a rise in blood pressure,[9] and in SURMOUNT-1 tirzepatide reduced

24-h ambulatory systolic blood pressure.[10] What is missing are trials designed specifically around blood-pressure endpoints—in particular in resistant hypertension—with medication reduction or durable remission as the primary outcome.

Cardiovascular conditions

Atherosclerotic cardiovascular disease

In general, there is abundant evidence associating excess weight with greater atherosclerotic cardiovascular disease (ASCVD) risk and cardiovascular death (table 1; appendix

	Epidemiological associations	Genetic data	Interventions		Need for future trials or wider context	Selected key trials (intervention; follow-up)
			Observational or non-randomised	Randomised		
Type 2 diabetes and pre-diabetes	++++	++++	++++	+++	The ability to reach remission of type 2 diabetes through low-calorie diets is well established, and this treatment is now offered in clinical care in several countries; reversion to normoglycaemia, and prevention of type 2 diabetes, have also been shown with GLP-1 receptor agonists and dual GLP-1 and GIP receptor agonists; however, more trials are needed to determine the broader benefits of sustained weight loss via incretin therapies over several years on complications and to assess the cost-effectiveness of such interventions; the evidence base for weight loss in pre-diabetes is also now strong, but more trials would help, including for how long type 2 diabetes can be prevented	DiRECT (diet; 12 months);[5] DIADEM-I (diet; 12 months);[6] STANDby (diet; 3–5 months);[7] SURMOUNT-1 (tirzepatide; 176 weeks)[8]
Hypertension	+++	+++	++++	++	Intentional weight loss consistently lowers blood pressure across dietary, pharmacological, and surgical approaches; few large-scale trials have specifically targeted resistant hypertension to assess medication reduction or durable remission	DiRECT secondary paper (diet; 20 weeks, 12 months, and 24 months);[9] SURMOUNT-1 (tirzepatide; 36 weeks)[10]
HFpEF	+++	+++	++	++	Data from lifestyle interventions (albeit scarce) and obesity medication trials suggest meaningful improvements in KCCQ scores with large-scale weight loss; in SECRET, caloric restriction improved peak oxygen uptake, KCCQ scores, and reduced bodyweight, left ventricular mass, and CRP; in STEP-HFpEF and STEP-HFpEF DM, semaglutide improved KCCQ-CSS scores, 6-minute walk distance, and reduced bodyweight, CRP, and NT-proBNP levels; in meta-analysis of SELECT, FLOW, and the STEP-HFpEF Program, semaglutide reduced the risk of the combined endpoint of cardiovascular death or worsening heart failure events; in SUMMIT, tirzepatide reduced the risk of heart failure outcomes (urgent visit or hospitalisation due to heart failure, oral diuretic intensification, or cardiovascular death), with additional benefits in KCCQ-CSS scores, 6-minute walk distance, CRP, and bodyweight; there is a need for long-term lifestyle trials, alongside obesity medications, as well as outcome trials with incretins	SECRET (diet; 20 weeks);[11] STEP-HFpEF (semaglutide; 52 weeks);[12] STEP-HFpEF DM (semaglutide; 52 weeks);[13] SUMMIT (tirzepatide; 52 weeks)[14]
HFrEF	++	++	+	+/–	Data from lifestyle trials are scarce and the few available trials are small, so disease-modifying effects of weight loss remain unproven; there is a need for large-scale dietary trials to assess the effects on KCCQ scores; there is a need for obesity medication trials examining effects on KCCQ scores, ideally alongside hard clinical outcomes	None
Atherosclerotic cardiovascular disease	++	++	++	++*	Likely need very long-term weight loss in a trial with dietary methods to prove that this lowers myocardial infarction or stroke, but this might be too challenging; SELECT showed a 20% reduction in MACE with semaglutide compared with placebo with around one-third of that benefit possibly linked to a reduction in waist circumference; more such data are needed in forthcoming trials of incretin-based and related agents	SELECT secondary paper (semaglutide; 20 weeks and 104 weeks)[15]
Microvascular angina	++	+	+	+	No large-scale trials have been sufficiently powered to evaluate patient-reported outcomes, changes in chest pain, need for medicines, and quality of life over at least 1 year with obesity medications	None
Atrial fibrillation	+++	++	+	+	There is a scarcity of trials of weight loss in people with atrial fibrillation; more trials are needed to investigate remission in atrial fibrillation and obesity; weight loss trials before or after cardioversion or ablation are needed to assess relevant outcomes (eg, atrial fibrillation recurrence and symptom burden)	LOSE-AF (diet and behavioural support program; 8 months)[16]
Stroke	++	++	+	++	Observational data show that bariatric surgery is associated with reduced stroke risk; SELECT showed a 20% reduction in MACE with semaglutide compared with placebo; a recently completed tirzepatide trial (SURPASS-CVOT) suggests cardiovascular benefit in type 2 diabetes; there is an ongoing trial with tirzepatide (SURMOUNT-MMO)	SELECT (semaglutide; 20 weeks and 104 weeks);[15] SURPASS-CVOT (tirzepatide *vs* dulaglutide);[17] SURMOUNT-MMO (tirzepatide; ongoing)[18]

(Table 1 continues on next page)

	Epidemiological associations	Genetic data	Interventions		Need for future trials or wider context	Selected key trials (intervention; follow-up)
			Observational or non-randomised	Randomised		
(Continued from previous page)						
PAD	+	+	+	+	Observational data suggest less functional decline with weight loss; the STRIDE trial showed semaglutide improved walking distance and quality of life in type 2 diabetes and PAD; there was a modest correlation between weight loss and improved outcomes, which suggests additional direct GLP-1 effects might be contributing to benefits; more data are needed on weight loss benefits in patients with PAD	STRIDE (semaglutide; 52 weeks)[19]
Aortic stenosis	++	+++	No data	No data	Weight loss trials are needed in those living with aortic stenosis and obesity, including those who have a BMI too high for surgery, with a focus on health-related quality of life outcomes	None

+/– shows minimal or conflicting evidence; + shows insufficient evidence (few or small studies, or studies at high risk of bias); ++ shows moderate evidence; +++ shows strong, consistent evidence; ++++ shows very strong evidence from multiple large, consistent studies; and no data shows no relevant studies identified. Ongoing trials in several of these areas are expected to strengthen the evidence base over the coming years. MACE are defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. CRP=C-reactive protein. CSS=clinical summary score. GIP=glucose-dependent insulinotropic polypeptide. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. KCCQ=Kansas City Cardiomyopathy Questionnaire. MACE=major adverse cardiovascular events. NT-proBNP=N-terminal pro-B-type natriuretic peptide. PAD=peripheral arterial disease. *Randomised evidence derives from cardiovascular outcome trials of incretin-based therapies, in which weight loss is only one of several contributing mechanisms; no trial of lifestyle or surgical weight loss has been powered for atherosclerotic cardiovascular disease events.

Table 1: **The strength of association between obesity and cardiometabolic conditions and the case for more trials in specific conditions**

pp 1–17).[53–55] These associations appear to be largely explained by intermediate risk factors (eg, systolic blood pressure, lipids, and diabetes). Although no robust trial evidence currently proves that intentional weight loss by lifestyle or surgical methods prevents ASCVD, observational evidence from bariatric surgery studies and post-hoc analyses of the Look AHEAD trial[56] provide some support for a link (although being post-hoc breaks randomisation), but further support is provided by genetic evidence.[53] However, as atherosclerosis occurs slowly, larger scale, sustained intentional weight loss over several years might be needed to definitively show its effect on lowering ASCVD risk.

Additionally, there is evidence suggesting potential benefits of intentional weight loss on stroke when examined separately (table 1; appendix pp 1–17).[57] Observational evidence suggests that higher BMI and other measures of central obesity are associated with increased risk of stroke; conversely, lower BMI is associated with a lower risk of both ischaemic and haemorrhagic stroke.[55–61] Genetic data from the UK Biobank show that genetically predicted fat mass index, more so than BMI, is associated with higher risk of ischaemic stroke.[53] Observational data also show that bariatric surgery is associated with a lower incidence of stroke.[57]

The large randomised controlled trial (RCT), SELECT, reported a 20% reduction in major adverse cardiovascular events (MACEs; a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in individuals with a BMI of 27 kg/m² or more and pre-existing cardiovascular disease (without diabetes) treated with semaglutide compared with placebo.[62] Semaglutide resulted in an average 9% weight loss compared with 0·9% weight loss with placebo. Data from SELECT suggested around a third of the reduction in MACE could be related to semaglutide-induced reduction in adiposity as captured by waist circumference change.[15] This means that most of the benefit of incretins in regard to MACEs might be direct rather than via weight reduction, as also implied by the results of the HARMONY Outcomes trial.[63] Similarly, SURMOUNT-MMO[18] is currently underway to assess the cardiovascular and wider morbidity and mortality benefits of tirzepatide, an agent with up to 20% average weight loss in trials.[64] This trial is notable as it is taking place in people without previous cardiovascular disease or diabetes. Results from SURPASS-CVOT show at least similar cardiovascular benefit with tirzepatide compared with the GLP-1 receptor agonist dulaglutide in people with type 2 diabetes and cardiovascular disease.[17]

Observational and genetic evidence also suggest excess weight is likely a causal factor for incident peripheral arterial disease (table 1; appendix pp 1–17).[53,65,66] In individuals with prevalent peripheral arterial disease, observational data suggest that intentional weight loss might help slow functional decline.[67] The STRIDE trial showed statistically significant and clinically meaningful improvements in walking distance, symptoms, and quality of life in those with type 2 diabetes and symptomatic peripheral arterial disease treated with semaglutide compared with placebo.[19] Weight loss correlated with improvement in walking distance, although this association was relatively modest as was the amount of weight loss (net 4 kg loss with semaglutide), suggesting semaglutide's direct antiatherosclerotic benefits might have a greater role than weight loss per se on hard atherosclerotic outcomes but that intentional weight loss might also benefit functional outcomes in some conditions such as peripheral arterial disease.

Heart failure

In general, the epidemiological and genetic links between adiposity and incident heart failure are approximately

twice as strong as the associations between obesity measures and ASCVD (table 1; appendix pp 1–17).[53,68] More recent multicohort evidence also suggests genetically determined BMI predicts adverse heart failure outcomes in people with prevalent heart failure across left ventricular ejection fraction of 40% or less and more than 40%.[69] Furthermore, unlike ASCVD, the connection between obesity and heart failure cannot be fully explained by

	Epidemiological associations	Genetic data	Interventions		Need for future trials or wider context	Selected key trials (intervention; follow-up)
			Observational or non-randomised	Randomised		
Psoriatic arthritis	++	++	++	+	Studies of intentional weight loss in psoriatic arthritis are insufficient in number and design but suggest that dietary weight loss of ≥5% improves disease outcomes in those initiated on TNF inhibitors, with greater benefits from greater weight loss; the effects of new obesity medications and bariatric surgery on psoriatic arthritis disease activity are not well studied, and more RCTs with these interventions are needed; TOGETHER-PsA provided the first insight for efficacy of dual GLP-1 and GIP receptor agonists alongside biologic use for treating psoriatic arthritis; more trials of obesity medications are needed earlier in disease course	TOGETHER-PsA (tirzepatide; 52-week trial, primary outcome at 36 weeks)[20]
Psoriasis	++	++	++	+	A meta-analysis[21] of RCT data indicates dietary weight loss, through low-calorie diet, in the order of 5–10% can improve psoriasis outcomes; bariatric surgery is associated with reduced incidence of psoriasis; however, there are few studies assessing obesity medications and/or bariatric surgery on psoriasis outcomes and more robust RCTs of these interventions in psoriasis with obesity are needed; TOGETHER-PsO is the first RCT to address the efficacy of dual GLP-1 and GIP receptor agonists alongside biologic use for treating psoriasis (showing modest skin modifying effect) and more trials of obesity medications are needed earlier in the disease course	TOGETHER-PsO (tirzepatide; 52-week trial, primary outcome at 36 weeks)[22]
Rheumatoid arthritis	+	+	+	+/–	Data on the effects of weight loss in the management of rheumatoid arthritis are currently scarce, limited mainly to observational studies, with one small RCT suggesting potential benefit on disease activity; larger RCTs are required in those with rheumatoid arthritis living with obesity	None
Gout	+++	+++	++	+	A systematic review[23] of dietary or surgical weight loss interventions favours intentional weight loss for individuals with gout and overweight or obesity; however, the existing evidence base is of low quality (few, mainly observational, studies of low methodological quality); large RCTs are needed to provide robust evidence for weight loss interventions as an integral part of gout management; post-hoc analysis of an RCT suggested tirzepatide could lower uric acid by around 14% more than placebo at the 15 mg dose in parallel with weight loss[24]	None
Osteoarthritis	+++	+++	++	++	Both observational and RCT evidence shows the beneficial effects of weight loss on reducing pain, stiffness, and improving function in osteoarthritis	STEP 9 (semaglutide; 68 weeks)[25]
Asthma	++	++	+	+	Observational data suggest bariatric surgery might be associated with beneficial outcomes in asthma; however, RCT evidence is currently lacking; a systematic review[26] of RCTs of predominantly lifestyle weight-loss interventions suggested weight loss improves asthma control and forced expiratory volume in 1 s; it is likely weight loss of at least 10% is needed for clinically meaningful improvement in asthma control; such weight loss can be reached with newer GLP-1 receptor agonists and dual GLP-1 and GIP receptor agonists, and observational data suggest GLP-1 receptor agonists might be associated with improved asthma control for people with obesity; larger, better quality RCTs of interventions with greater weight loss, such as those that can be reached with low-calorie diet and GLP-1 receptor agonist therapies, are required; trials testing the impact of these medicines on the rate of acute exacerbations due to infections are also needed	None
COPD	++	++	+	+/–	There are few clinical studies investigating intentional weight loss in COPD; although a small proof of concept study[27] suggested improvements in clinical outcomes with a weight reduction programme of low-energy diet and exercise training, a larger RCT[28] of a different low intensity lifestyle programme did not improve the odds of reaching clinically meaningful improvements in walking distance or breathlessness; however, this might have related to the modest amount of weight loss (adjusted between group treatment difference of 1·34 kg) in the larger RCT; data on GLP-1 receptor agonist therapies in COPD are scarce; one small, randomised trial[29] of 40 individuals with obesity and COPD treated with liraglutide showed improvement in some pulmonary function measures and health status; larger RCTs with greater weight loss are needed to robustly answer whether targeted weight loss in COPD with obesity will improve disease outcomes, including the rates of acute exacerbations	None
OSA	+++	+++	++	++	Weight reduction via lifestyle, pharmacological, or surgical intervention is associated with improvements in severity of OSA	SURMOUNT-OSA (tirzepatide; 52 weeks)[30]

(Table 2 continues on next page)

	Epidemiological associations	Genetic data	Interventions		Need for future trials or wider context	Selected key trials (intervention; follow-up)
			Observational or non-randomised	Randomised		
(Continued from previous page)						
GORD	+++	+++	++	+	A structured weight loss programme improved GORD symptoms and percentage bodyweight loss correlated with reduction in GORD symptoms;[31] few RCTs show that diet improves GORD symptoms; few RCTs show that bariatric surgery reduced reflux symptoms; incretin-based obesity medications that slow gastric emptying increase GORD in the short term; data on GORD prevalence beyond 1 year are scarce, which matters because any short-term increase in reflux driven by delayed gastric emptying might, with continued treatment, be offset by the benefits of sustained weight loss; data on GORD with newer obesity medications that are not GLP-1 receptor agonist-based (eg, amylin) are of interest	None
MASLD and MASH	+++	+++	++	+++	Several studies show that orlistat improves liver function; in cohort studies, bariatric surgery leads to MASLD resolution; bariatric surgery is effective for histological resolution of MASH; weight-loss interventions (eg, behavioural, drugs, or surgery) improve alanine aminotransferase levels, steatosis, MASLD activity scores, and MASH; time-restricted eating did not improve MASLD (TREATY-FLD); RCTs of semaglutide show beneficial histological, radiological, liver enzyme, and cardiometabolic effects; there appears to be greater liver fat reduction with efinopegdutide (a GLP-1–glucagon receptor co-agonist) *vs* semaglutide; a few other trials show broadly similar results in terms of reduction in steatosis and fibrosis	TREATY-FLD (diet; 12 months);[32] BRAVES (surgery; 1 year);[33] MK-6024 P001 (efinopegdutide; 24 weeks);[34] SYNERGY-NASH (tirzepatide; 52 weeks);[35] 1404-0043 (survodutide; 48 weeks);[36] J1I-MC-GZBF (retatrutide; 48 weeks);[37] ESSENCE (semaglutide; 72 weeks)[38]
Depression	++	++	++	+	In longitudinal studies, weight loss reduced depressive symptoms; from a meta-analysis of RCTs, diet reduced depression scores, but exercise and mostly older GLP-1 receptor agonists (eg, dulaglutide, exenatide, liraglutide, lixisenatide, and lower-dose semaglutide) with modest weight loss did not affect depression[39–41]	None
Fibromyalgia	++	+	+	+/–	Obesity is prevalent in fibromyalgia, can increase the risk of developing fibromyalgia, and associates with worse symptoms; preliminary evidence suggests intentional weight loss might improve fibromyalgia symptoms; additional evidence from a weight loss trial[42] in post-COVID-19 condition supports reduced fatigue with low-calorie diet weight loss; larger RCTs of weight loss interventions including dietary and pharmacological approaches (eg, with GLP-1 receptor agonist) in fibromyalgia are needed	None, though reduced fatigue in ReDIRECT (diet; 6 months)[42]

+/– shows minimal or conflicting evidence; + shows insufficient evidence (few or small studies, or studies at high risk of bias); ++ shows moderate evidence; +++ shows strong, consistent evidence; ++++ shows very strong evidence from multiple large, consistent studies; and no data shows no relevant studies identified. Ongoing trials in several of these areas are expected to strengthen the evidence base over the coming years. COPD=chronic obstructive pulmonary disease. GIP=glucose-dependent insulinotropic polypeptide. GORD=gastro-oesophageal reflux disease. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. OSA=obstructive sleep apnoea. RCTs=randomised controlled trials.

Table 2: **The strength of association between obesity and rheumatological, respiratory, and gastrointestinal disorders, depression, and fibromyalgia—existing data and areas for more trials**

intermediate risk factors. Ample observational evidence from bariatric surgery studies supports the benefits of weight loss in preventing incident heart failure and improving outcomes in patients with prevalent heart failure.[70,71] Small lifestyle weight-loss intervention trials in HFpEF have shown that caloric restriction can improve peak oxygen uptake and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, reduce left ventricular mass by MRI, and lower C-reactive protein.[11,72] Emerging trial evidence from the STEP-HFpEF,[73] STEP-HFpEF DM,[13] SELECT,[62] and FLOW[74] trials suggests that weight loss with semaglutide offers benefits in patients with heart failure with mildly reduced and preserved ejection fraction, including potentially a reduced risk of the composite endpoint of cardiovascular death or worsening heart failure events.[75] Consistent with these findings, the SUMMIT trial provided preliminary evidence that tirzepatide reduced the risk of the composite of cardiovascular death or worsening heart failure compared with placebo in patients with possible HFpEF.[76]

The STEP-HFpEF trials, combined with SUMMIT, showed that weight loss is strongly linked to KCCQ Clinical Summary Score benefits, but more data are needed from larger outcome trials to test the relative contribution of weight loss per se on harder outcomes.[12,14] Fortunately, such trials are ongoing: MARITIME-HF (NCT07037459)[77] is comparing maridebart cafraglutide with placebo for the composite of cardiovascular death or heart failure events in 5056 patients with obesity and heart failure with preserved or mildly reduced ejection fraction, and HF-POLARIS (NCT07567001)[78] is evaluating zenagamtide (formerly amycretin) for the same

composite outcome in 5610 patients with this clinical phenotype.

Although pilot data suggest similar benefits of weight loss in heart failure with reduced ejection fraction, there is a clear scarcity of large-scale trials, with existing studies focused mainly on short-term lifestyle weight loss rather than pharmacological approaches.[79–82] Clearly, more data will be forthcoming, but notably, the benefits of weight loss might emerge relatively quickly, as favourable cardiac remodelling has been observed within about 20 weeks of dietary weight loss.[11,72]

Other cardiovascular conditions

Microvascular angina

Microvascular dysfunction, the distinguishing characteristic of microvascular angina (also called ischaemia with non-obstructive coronary arteries), has been associated with obesity in both prospective and cross-sectional studies (table 1; appendix pp 1–17).[83–85] Emerging trial evidence suggests that weight loss, or therapies that improve metabolic health (eg, metformin, which has only modest effects on bodyweight), might help reduce angina burden in patients with microvascular angina. However, larger and longer-term trials are needed, especially for a condition with few effective therapeutic options.

Atrial fibrillation

Ample observational and genetic evidence supports a likely causal association between higher BMI and incident atrial fibrillation (table 1; appendix pp 1–17).[53] Scarce observational evidence from bariatric surgery suggests that weight loss might prevent incident atrial fibrillation, perhaps particularly in younger individuals and those with higher blood pressure.[86] However, meta-analyses, albeit with small total event numbers, did not show a difference in incident atrial fibrillation with tirzepatide.[87,88]

Although some small, short-term trials suggest that modest weight loss might benefit patients with prevalent atrial fibrillation, larger and longer-duration trials would be useful particularly with interventions that give more than 10–15% weight loss. These should also consider examining cost benefits, such as preventing expensive procedures (eg, ablation), reducing recurrence rates (eg, after cardioversion or ablation), or lowering complications from such procedures. Preliminary data from SELECT suggested semaglutide reduced atrial fibrillation events, irrespective of history of atrial fibrillation status.[89]

Taken together, alongside the modest resting heart rate increase observed across incretin-based therapies (a recognised class effect, with mean increases of roughly 2–3 bpm for tirzepatide and semaglutide), the current evidence suggests ongoing equipoise.[90] There is therefore a need for dedicated trials in populations with prevalent atrial fibrillation, where effects on atrial fibrillation burden, progression, and related clinical outcomes can be more robustly assessed.

Aortic stenosis

Robust observational and genetic evidence supports a causal link between obesity and the clinical presentation of aortic stenosis (table 1; appendix pp 1–17).[53] However, evidence that weight loss benefits the prevention or treatment of aortic stenosis is scarce, with only small retrospective series suggesting that bariatric surgery might be feasible and safe as a bridge to subsequent aortic valve replacement.[91]

Common skin and musculoskeletal conditions

Psoriasis

Epidemiology and genetic studies show that excess weight is causally associated with greater risk of developing psoriasis (table 2; appendix pp 18–27).[92,93] For every 1 unit increase in BMI, it is estimated the odds of developing psoriasis increase by 9%.[92] Although the exact mechanisms remain unknown, it is thought that obesity promotes a pro-inflammatory state, increasing susceptibility to developing psoriasis and being associated with more severe skin disease.[94] Excess weight is associated with poorer response to systemic psoriasis treatments, with the odds of reaching a 90% improvement in Psoriasis Area and Severity Index (PASI 90) being 30% lower in those with obesity compared with those without obesity, treated with biologic agents.[95] There is accumulating evidence for the benefits of weight loss in the management of psoriasis with obesity. Meta-analysis of RCTs assessing dietary weight loss in psoriasis and obesity revealed that those given a low-calorie diet were 47% more likely to reach a 75% improvement in Psoriasis Area and Severity Index (PASI 75) compared with those not given a low-calorie diet.[21] To date, there are few data on the effects of pharmaceutical and surgical weight-loss interventions in managing psoriasis with obesity. Small case series suggest a potential beneficial effect on reducing psoriasis disease activity with GLP-1 receptor agonists.[96,97] The 2026 TOGETHER-PsO clinical trial provided the first RCT evidence of the efficacy of tirzepatide, alongside ixekizumab (a monoclonal antibody IL-17A inhibitor), on disease activity in psoriasis, with evidence of a modest skin modifying effect of tirzepatide.[22] Clearly, additional trials are needed, including earlier in the disease course. Observational cohort studies have shown an association between bariatric surgery and lower incidence of psoriasis, in particular between gastric bypass surgery and lower incidence of psoriasis and psoriatic arthritis.[98] However, there are no RCTs assessing the effect of bariatric surgery on psoriasis incidence or severity.

Psoriatic arthritis

20–30% of people with psoriasis develop the chronic inflammatory arthritis psoriatic arthritis.[99] Obesity is a key risk factor for progression of psoriasis to psoriatic arthritis

(table 2; appendix pp 18–27).[100] The prevalence of obesity is elevated in psoriatic arthritis, with the average BMI now approaching 30 kg/m². Mendelian randomisation suggests that elevated BMI might causally contribute to increased risk of psoriatic arthritis, whereas the reverse (ie, genetic liability to psoriatic arthritis or psoriasis) did not predict BMI.[101] It is postulated that obesity plays a key pathogenic role in psoriatic arthritis through shared immunological pathways (eg, TNF, IL-23, and IL-17), and mechanical loading, which might lead to stress and microdamage to tendons and entheses. Obesity is associated with worse psoriatic arthritis disease activity,[102] and diminished response to TNF-inhibitors.[103,104] The site of fat storage in psoriatic arthritis appears important when assessing cardiometabolic risk. Individuals with psoriatic arthritis have been shown to store more fat in visceral and liver compartments compared with age-matched, sex-matched, and BMI-matched controls.[105] This fat distribution is associated with greater propensity to type 2 diabetes and coronary heart disease.[105]

Although studies of intentional weight loss in psoriatic arthritis are scarce, evidence from low-calorie dietary interventions has shown that weight loss of 5% or more is associated with improved disease activity and response to TNF-inhibitors.[106,107] The 2026 TOGETHER-PsA trial of tirzepatide alongside ixekizumab provided the first clinical trial evidence for the efficacy of weight loss, via dual GLP-1 and GIP receptor agonism, on disease activity in psoriatic arthritis, with evidence of a modest additional benefit of tirzepatide.[20] Postulated benefits of tirzepatide in psoriatic arthritis might be due to a combination of weight loss (ie, indirect effects) as well as possible direct effects of GLP-1 receptor agonism in the joint.[108]

Taken collectively, and together with the known health benefits of weight loss on managing blood pressure, lipids, and glucose control, intentional weight loss of 5% or more in those with psoriatic arthritis and overweight or obesity is likely beneficial for both psoriatic arthritis and its associated cardiometabolic comorbidities. A series of trials at differing stages of psoriatic arthritis would be useful, as would trials of agents that yield differing amounts of weight loss.

Gout

There is a strong relationship between obesity and gout (table 2; appendix pp 18–27).[109,110] Individuals with gout have on average around three units higher BMI at diagnosis compared with those without gout, and this likely contributes at least in part to greater cardiovascular risk.[111] Genetic studies have shown that higher adiposity-associated single nucleotide polymorphisms predict hyperuricaemia and gout.[112] A one SD (4·6 kg/m²) increase in genetically predicted BMI was associated with more than double the odds of gout (odds ratio [OR] 2·24, 95% CI 1·70–2·95). It is thought that elevated serum uric acid might be more likely a consequence of rather than a cause of obesity.[113] Obesity has also been shown to increase the risk of recurrent gout attacks.[114] European and US guidelines recommend weight loss as part of the management of gout and its associated cardiometabolic comorbidities.[115,116] However, surprisingly, the existing evidence for weight loss interventions in treating gout is limited to mainly non-randomised studies of low quality.[23] One small proof of concept RCT of 16 weeks of low-calorie diet showed substantial weight loss, with a trend towards lower serum urate levels and improvements in fatigue scores, although between-group differences were not statistically significant.[117] A 2026 post-hoc analysis of the SURMOUNT-1 trial showed that tirzepatide lowered uric acid by around 14% more than placebo at the 15 mg dose, with analyses suggesting this change occurs primarily via weight loss.[24] Given the rising prevalence of overweight and obesity, their likely causal role in contributing to gout pathogenesis and associated comorbidities, and many individuals not reaching serum urate targets with existing therapies, there is an urgent need for larger, robust RCTs to cement weight loss as a key component of gout management. Such trials could usefully examine benefits in those also prescribed sodium-glucose cotransporter 2 inhibitors, which can also lower urate levels.

Rheumatoid arthritis

Before the advent of effective biological therapies for rheumatoid arthritis, this chronic inflammatory arthritis was often associated with cachexia (ie, unintentional weight loss). However, with effective disease-modifying therapies now available, and the rising prevalence of obesity, the adverse impact of excess weight in rheumatoid arthritis, and indeed many rheumatic and musculoskeletal diseases, has now become apparent (table 2; appendix pp 18–27).[118] Although less strongly related to obesity than psoriasis, psoriatic arthritis, and gout, meta-analysis of observational studies revealed that overweight (pooled risk ratio 1·12, 95% CI 1·04–1·20) and obesity (1·23, 1·09–1·39) were each associated with an increased risk of developing rheumatoid arthritis compared with healthy weight.[119] These observations are supported by genetic studies that show the risk of rheumatoid arthritis increased by 22% for a one SD (4·8 kg/m²) increment in genetically predicted BMI (OR 1·22, 95% CI 1·09–1·37).[120] Obesity has also been associated with reduced therapeutic response to anti-TNF agents in rheumatoid arthritis,[121,122] and lower remission rates.[123]

Although observational studies suggest weight loss might reduce rheumatoid arthritis disease activity,[124,125] RCT evidence is scarce in this area. One small proof of concept RCT in 40 patients with rheumatoid arthritis randomised to hypocaloric diet or control showed a mean weight loss of 9·5 kg with dietary intervention and trends towards improvements in disease activity and activities of daily living.[126] Although these studies are encouraging, larger prospective controlled trials at differing disease stages are needed to establish weight loss as part of routine management in rheumatoid arthritis with obesity,

as the prevalence of obesity in people with rheumatoid arthritis will progressively rise.

Osteoarthritis

Obesity is a major risk factor for development and progression of osteoarthritis, with observational data showing an over four-fold higher risk of developing knee osteoarthritis in those living with class II obesity or greater (defined as BMI ≥35 kg/m²) compared with those with normal weight (table 2).[127] Mendelian randomisation analysis provides further evidence that excess adiposity is causal in development of osteoarthritis, likely through predominantly mechanical effects.[128] Obesity is associated with more pain and worse physical function in knee osteoarthritis.[129] Intentional weight loss is a key component in the management of knee osteoarthritis. A large network meta-analysis revealed that the most effective weight-loss interventions for reducing pain in knee osteoarthritis were bariatric surgery, low-calorie diet plus exercise, and intensive weight loss plus exercise.[130] On combining study results, for every 1% weight loss, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, function, and stiffness scores decreased by about 2% (lower scores indicate less pain, less stiffness, and improved function). The meta-analysis showed that significantly reducing knee pain and stiffness and improving physical function requires substantial weight loss, with 25% weight reduction necessary to obtain a 50% reduction in knee pain and stiffness.[130] Of note, this meta-analysis did not include GLP-1 or dual GLP-1 and GIP receptor agonists.

In 2024, the STEP 9 trial was the first RCT to assess the efficacy of once-weekly semaglutide in individuals with obesity and knee osteoarthritis.[25] This study showed an average weight loss of 13·7% with semaglutide compared with 3·2% weight loss with placebo over 68 weeks, with both groups receiving dietary and physical activity counselling. Semaglutide was associated with significantly greater and clinically meaningful improvements in knee pain, with WOMAC pain scores improving by 41·7 points compared with 27·5 points with placebo (estimated between-group difference of 14·1 points; ~20% relative reduction from baseline; p<0·001), alongside greater improvements in physical function and reduced use of analgesic agents. Although the trial was not designed to assess the mechanism by which semaglutide improved pain in knee osteoarthritis, the substantial weight loss from semaglutide is likely a major contributor to reducing mechanical stress on the knee joints. It is also possible that GLP-1 receptor agonists might have direct anti-inflammatory and anti-degradative effects in the joints, but more data are now needed to prove such effects.[108]

Respiratory conditions

Asthma

Obesity is associated with a greater risk of developing asthma, with observational studies showing a graded association between increasing BMI and odds of incident asthma (table 2; appendix pp 28–34).[131] Genetic studies suggest a causal association between BMI and asthma development, with a genetically predicted 4·1 kg/m² increase in BMI associated with 49% greater odds of doctor-diagnosed asthma.[132] Obesity has been associated with poorer response to glucocorticoids,[133] poorer asthma control,[134] greater use of controller medications, and more days missed from work related to asthma,[135] compared with those with a BMI of less than 25 kg/m². Evidence suggests people living with obesity are less likely to obtain asthma remission.[135] Intentional weight loss might improve asthma management through a variety of potential mechanisms, including improved lung mechanics and reductions in inflammation.[136]

Observational studies of individuals with obesity and asthma undergoing bariatric surgery suggest weight loss is associated with reductions in systemic and airway pro-inflammatory markers,[137] improvement in some lung function parameters,[138] and less asthma medication use.[139] However, these studies are limited by their retrospective nature, often small sample sizes, and absence of control groups. RCTs of intentional weight loss with dietary and physical activity interventions in asthma suggest weight loss might improve asthma control and lung function as assessed by forced expiratory volume in 1 s.[26] It has been suggested that weight loss of 10% or more might be required to produce clinically meaningful improvements in asthma.[140] Such sizeable weight loss can now be reached with newer incretin-based therapies including semaglutide and tirzepatide, and observational data suggest GLP-1 receptor agonists might be associated with improved asthma control for people with obesity.[141] It is postulated that GLP-1 receptor agonist therapies might have additional anti-inflammatory effects in the lungs beyond weight loss.[136] Larger and better quality RCTs of interventions with greater weight loss, such as low-calorie diet and GLP-1 receptor agonist therapies, are now needed to incorporate weight loss into treatment guidelines for managing asthma with obesity.

Chronic obstructive pulmonary disease

Observational data show the prevalence of chronic obstructive pulmonary disease (COPD) increases with BMI, with the odds of COPD more than three-fold higher in men and four-fold higher in women, with class III obesity (defined as BMI ≥40 kg/m²) compared with those of a healthy weight (table 2; appendix pp 28–34).[142] Larger waist circumference and waist-to-hip ratio, reflective of greater central adiposity, are associated with greater risk of incident COPD.[143,144]

Genetic studies further support a causal role of obesity in the risk of developing COPD.[145–147] There are few clinical studies investigating intentional weight loss in managing COPD with obesity. The INSIGHT COPD clinical trial showed patients randomised to a lifestyle intervention (as per the Diabetes Prevention Program's Lifestyle

Balance curriculum) for 12 months had improvements in walking distance and were less breathless than controls; however, this did not reach clinically meaningful improvements.[28] These results might have been related to the modest weight loss reached with the intervention. A smaller proof of concept study investigating the effects of a low-energy diet, dietary counselling, and exercise showed promise with improvements in numerous clinical outcomes including exercise capacity, dyspnoea, strength, and functional outcomes with an average reduction in BMI of 2·4 kg/m².[27] However, this study was limited by a small sample size and absence of control group. Data on new GLP-1 receptor agonist therapies in COPD are scarce, with one small, randomised trial of 40 individuals with obesity and COPD treated with liraglutide showing an improvement in some pulmonary function measures and health status.[29] There is a need for larger RCTs of these and other more efficacious weight-loss interventions to assess their true effect on management of COPD with obesity.

Obstructive sleep apnoea

Obesity is a major risk factor for obstructive sleep apnoea (OSA; table 2).[148–150] Observational data show a 5 kg/m² higher BMI is associated with 60% greater odds of sleep-disordered breathing.[148] Relative to maintaining stable weight, a 10% weight gain predicts a six-fold increase in the odds of developing moderate to severe sleep-disordered breathing.[149] Genetic analysis further supports a causal link between obesity and OSA.[150] The mechanisms linking obesity to OSA are complex. Excess adiposity might directly affect the anatomy of the upper airway as fat is deposited in surrounding structures, increasing the likelihood of airway collapse. Excess fat deposited in the tongue might also contribute, impairing genioglossus muscle function.[151] Supporting this hypothesis, a study investigating intentional weight loss with intensive lifestyle or bariatric surgery showed that a reduction in tongue fat was a key mediator in improving OSA.[152] There is clear evidence that weight loss improves outcomes in OSA. The Sleep AHEAD study showed that weight loss with an intensive lifestyle intervention of reduced calorie intake (1200–1500 kcal/day) and 175 min per week of moderate-intensity activity resulted in fewer apnoea-hypopnoea index events and greater rates of OSA remission compared with standard education sessions, with a weight loss of 10 kg or more associated with the greatest reductions in apnoea-hypopnoea index.[153] A systematic meta-analysis of 27 studies of weight loss via bariatric surgery, diet and exercise, or pharmacological interventions further supports weight loss to improve OSA with a 20% reduction in BMI associated with a decrease in apnoea-hypopnoea index of 57%.[154] The 2024 SURMOUNT-OSA study showed that tirzepatide treatment resulted in an average 16–17% additional weight loss compared with placebo with substantially improved sleep apnoea-related symptoms.[30] Up to 50% of participants treated with tirzepatide had enough symptom relief to fall below disease thresholds typically required for positive airway pressure therapy. Significant reductions in blood pressure and high-sensitivity C-reactive protein were also seen with tirzepatide.[30] As such, weight management is a key component of clinical guidelines for management of OSA.[155]

Gastrointestinal conditions

Gastro-oesophageal reflux disease

Observational studies consistently show that higher BMI is associated with an increased risk of gastro-oesophageal reflux disease (GORD), with abdominal obesity also associated with reflux oesophagitis (table 2; appendix pp 35–41).[156,157] Genetic data from large-scale genome-wide association studies combining the UK Biobank, the FinnGen study, and consortia of individuals of European ancestry show that genetically predicted higher adulthood BMI and waist-to-hip ratio are associated with an increased risk of GORD.[158] Observational data from structured weight-loss programmes (incorporating diet, physical activity, and behaviour change) reveal a significant correlation between percentage bodyweight loss and reductions in GORD symptoms.[31] Additionally, RCTs focusing on dietary interventions have shown that low-calorie diets improve GORD symptoms,[159,160] and bariatric surgery (specifically Roux-en-Y gastric bypass but not sleeve gastrectomy) RCTs show a reduction in reflux symptoms following surgery.[161] By contrast, due to their mechanisms of action, which include slowing of gastric emptying, GLP-1 receptor agonists have been shown to increase the prevalence of GORD by around two-fold relative to placebo.[162] Longer-term trial follow-up is also needed to better characterise gastrointestinal outcomes, as these therapies have meaningful effects on both caloric intake and gastric emptying. Although short-term gastrointestinal symptoms are well recognised and often attenuate over time, the potential for long-term benefits or harms with sustained use remains insufficiently defined.

MASLD and metabolic dysfunction-associated steatohepatitis

Epidemiological data show that the risk of MASLD and metabolic dysfunction-associated steatohepatitis (MASH) increases linearly with BMI, with a 5–9-fold increase in risk at a BMI of 30–32·5 kg/m² compared with 20–22·5 kg/m² (table 2; appendix pp 35–41).[163] Among individuals living with obesity, there is a high prevalence of MASLD (75%), of which most is steatosis without steatohepatitis (43%), with MASH present in 34%.[164] Furthermore, hepatic steatosis is found in 65% of people with class I–II obesity (defined as BMI 30–39·9 kg/m²).[165] Controlled trials involving individuals with MASLD show a dose–response relationship between the degree of calorie restriction and beneficial effects on liver function and weight loss.[166] Evidence from RCTs and single-arm trials shows that orlistat is associated with improvements in

liver enzymes and reductions in BMI.[167] Cohort studies show that bariatric surgery is associated with biopsy-confirmed resolution of non-alcoholic fatty liver disease (now MASLD).[168] RCTs of weight loss interventions (including behavioural, pharmacological, or surgical) consistently show that weight loss is associated with improved biomarkers (eg, alanine aminotransferase), reductions in histologically or radiologically measured liver steatosis, improved histological MASLD activity score, and resolution of MASH.[169] RCTs in MASLD show that semaglutide treatment is associated with beneficial histological, radiological, liver enzyme, and cardiometabolic effects.[170] Trials of other incretin agents now suggest broadly similar benefit. In the phase 2 SYNERGY-NASH trial, tirzepatide was associated with increased resolution of MASH.[35] Additionally, RCT evidence for efinopegdutide (a GLP-1–glucagon receptor co-agonist) shows significantly greater reductions in liver fat content compared with semaglutide.[34] The BRAVES open-label randomised trial of 288 participants found that bariatric surgery is effective in reaching histological resolution of MASH.[33]

Mental health and other conditions

Depression

Epidemiological data consistently show a link between obesity and an increased risk of depression, including major depressive disorder (table 2; appendix pp 42–49).[171–173] Genetic evidence from multiple Mendelian randomisation studies suggests that higher BMI or waist-to-hip ratio is causally associated with an elevated risk of depression, with meta-analyses reporting approximately 33% higher odds among individuals genetically predisposed to obesity (OR ~1·33).[174,175] Longitudinal studies suggest that weight loss—whether through diet or behavioural training—is associated with fewer depressive symptoms.[176] Meta-analyses of RCTs show that low-calorie diets are significantly associated with lower depression scores, whereas no significant effects have been observed with exercise or GLP-1 receptor agonists.[39–41] Evidence for GLP-1 receptor agonists is derived largely from older agents (eg, dulaglutide, exenatide, liraglutide, lixisenatide, and lower-dose semaglutide) studied in type 2 diabetes and overweight or obesity, with minimal trial data to date on newer agents in studies specifically designed to assess depression outcomes in people living with both obesity and depression, although at least one such trial is ongoing (SEMAMOOD; NCT07136714).[41,177]

Fibromyalgia

Fibromyalgia is common and has an incompletely understood cause. There are potential inflammatory drivers, but both fatigue and chronic pain might drive further weight gain, especially with people now living in more obesogenic environments. Epidemiological data report that more than 1 in 3 people with fibromyalgia live with obesity, increasing to more than 4 in 10 in the USA (table 2; appendix pp 42–49).[178] Obesity increases the risk of developing fibromyalgia[179] and might worsen several key domains including pain, fatigue, sleep disturbance, and quality of life.[178] A Mendelian randomisation study suggested obesity is causally associated with development of fibromyalgia.[180] Preliminary evidence suggests intentional weight loss, whether via a behavioural weight-management programme,[181] calorie-restricted diet,[182,183] or bariatric surgery,[184] might improve symptoms in fibromyalgia, although only one of these studies included a control group, and the majority were of small sample size, limiting their wider applicability. A large propensity score-matched TriNetX cohort study found that GLP-1 receptor agonist use was associated with reduced opioid prescribing and lower rates of pain-related and fatigue-related diagnostic codes in fibromyalgia, suggesting a lower symptom burden.[185] However, these observational findings require confirmation via RCTs. Preliminary evidence from a low-calorie diet intervention in individuals with post-COVID-19 condition (also known as long COVID) and obesity suggested that weight loss improves fatigue, acknowledging that fatigue with long COVID might not necessarily be similar to the fatigue in fibromyalgia.[42] There is a need for more robust studies of weight-loss agents that might offer both anti-inflammatory and other weight loss benefits.

Conditions not considered but warranting future trials

Several conditions fall outside the scope of this brief Review but merit dedicated trials. We have deliberately not discussed many female-specific conditions, including pregnancy-related complications (eg, gestational diabetes and pre-eclampsia), polyendocrine metabolic ovarian syndrome (formerly polycystic ovary syndrome),[186] and menopause, which warrant focused reviews from topic experts. We also excluded other conditions in which obesity is strongly implicated but which are less common, such as idiopathic intracranial hypertension or lymphoedema.

We also did not include cancer in this Review. For cancer, interventional evidence remains scarce and any benefits might take many years to emerge for most cancers. To our knowledge, there are currently no randomised trials showing that weight loss improves clinically meaningful cancer outcomes; most available data are observational and therefore potentially susceptible to bias. In addition, the marked heterogeneity across cancer types suggests this topic would be more appropriately addressed in a dedicated review.

We also did not consider dementia, largely due to the scarcity of trial evidence and the long prodromal phase of disease, which makes such trials challenging. That said, sustained, intentional weight loss in midlife might be expected to reduce incident dementia risk indirectly, given its beneficial effects on blood pressure, lipids, and diabetes, and—in the case of incretin therapies—cardiovascular disease, all recognised risk factors for dementia.

Future trial considerations

Several priorities emerge for the design of future trials evaluating weight-loss interventions across differing disease domains. First, there remains a need for high-quality randomised evidence to establish disease-specific treatment effects in a number of conditions where current data are scarce. Although some areas (eg, type 2 diabetes, HFpEF, MASLD and MASH, OSA, and osteoarthritis) already have robust trial support with some agents, many others require targeted evaluation, including studies conducted at different stages of disease progression and with differing agents.

Second, future trials should incorporate pre-specified mediation analyses to better disentangle weight-dependent from weight-independent effects, ideally using multiple adiposity measures. However, given the complexity of adiposity biology and interindividual variability, complementary approaches, such as comparing outcomes across trials of interventions that reach differing magnitudes of weight loss, could provide more robust insights.

Third, trial designs will need to evolve in response to the widespread availability of incretin-based therapies. Active comparator designs might be increasingly appropriate, and careful selection and validation of endpoints will be essential, particularly for slowly progressive conditions. Embedding mechanistic substudies, where feasible, would further strengthen knowledge and causal inference, increasing clinical motivation to tackle weight earlier in many conditions.

Fourth, there is a strong rationale for trials in multimorbid populations, with co-registration of multiple condition-specific endpoints (including many conditions considered in this Review) to better capture the cross-condition benefits of weight loss. Such approaches might more accurately reflect real-world clinical populations and inform treatment decisions across multiple co-existing diseases, aiding future cost-effectiveness analyses for important subgroups of people.

Fifth, it is important to establish whether short-term weight loss (whether reached through pharmacological therapy or lifestyle intervention) confers durable legacy effects. It is plausible that even transient weight reduction might favourably alter disease trajectories or delay progression in some conditions. However, this hypothesis remains insufficiently tested for many outcomes and requires dedicated trial evidence.

Sixth, and equally important, trials are needed in low-income and middle-income settings, including populations in whom disease onset occurs at lower BMI thresholds (eg, type 2 diabetes, which is substantially more prevalent at lower BMI levels in many non-White populations). Alongside this, scalable and affordable treatment strategies must be developed, without which the benefits described in this Review will accrue only to high-income populations.

Finally, future studies should account for variability in treatment response and therapeutic goals. The relationship between the extent of weight loss and clinical benefit is not uniform across conditions, and optimal targets will also depend on patient characteristics (including age, sex, and ethnicity), as well as disease stage, comorbidity burden, and individual preferences. Accordingly, weight-loss targets should be individualised.

Conclusions

By triangulating adiposity to outcome evidence from multiple angles (ie, epidemiological, genetic, observational, and randomised trial evidence) in differing conditions, this Review emphasises the central role of obesity in driving multimorbidity across cardiovascular, metabolic, musculoskeletal, respiratory, gastrointestinal, and mental health disorders. Structured weight-management programmes using low-calorie diets and behavioural support are now key components of type 2 diabetes remission and prevention strategies. However, similar systematic adoption of weight-loss interventions in other disease areas remains scarce, with clinical management often focused on downstream organ damage rather than the upstream driver of excess adiposity.

New weight-loss therapies, such as the GLP-1 receptor agonist semaglutide and the dual GLP-1 and GIP receptor agonist tirzepatide, reach average weight reductions of ~14–20% in people without type 2 diabetes and show benefits across many obesity-related conditions. These include cardiovascular diseases (eg, ASCVD, HFpEF, and hypertension), metabolic dysfunction (eg, type 2 diabetes, pre-diabetes, MASLD, and dyslipidaemia), musculoskeletal disease (eg, osteoarthritis), and respiratory disorders (eg, OSA). Their broad impact highlights the potential of targeting adiposity to improve multimorbidity.

Despite this, many other conditions in which obesity plays a major role still lack robust weight management components in their treatment pathways. These include musculoskeletal conditions such as psoriatic arthritis, gout, and to a lesser extent rheumatoid arthritis; respiratory conditions including asthma and COPD; cardiovascular conditions such as atrial fibrillation, ischaemia with non-obstructive coronary arteries, and aortic stenosis; and mental health disorders including depression. Fibromyalgia is also an example of a condition where such trials might be particularly informative, given the scarcity of current evidence and potential for weight loss to influence multiple symptom domains, perhaps particularly fatigue.

Large, rigorous randomised controlled trials of lifestyle, pharmacological, and surgical weight-loss strategies are therefore urgently needed to define potential disease-modifying effects. In addition, further trials targeting different disease stages are warranted, for example, in type 2 diabetes soon after diagnosis, where remission could be reached in a substantial proportion of individuals, and in the prevention of heart failure.

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Search strategy and selection criteria

References for this Review were primarily identified through PubMed searches for English language articles across epidemiology, genetics, and interventions published from Jan 1, 1990, to May 17, 2026, using the terms: ("weight loss" OR "GLP-1" OR "incretin" OR "bariatric surgery") AND ("causal" OR "Mendelian randomisation" OR "efficacy" OR "outcome") AND ("type 2 diabetes" OR "pre-diabetes" OR "hypertension" OR "cardiovascular disease" OR "stroke" OR "peripheral arterial disease" OR "heart failure" OR "microvascular angina" OR "atrial fibrillation" OR "aortic stenosis" OR "psoriasis" OR "psoriatic arthritis" OR "gout" OR "rheumatoid arthritis" OR "osteoarthritis" OR "asthma" OR "COPD" OR "obstructive sleep apnoea" OR "gastro-oesophageal reflux disease" OR "MASLD" OR "NAFLD" OR "MASH" OR "NASH" OR "depression" OR "fibromyalgia") AND ("randomised controlled trial" OR "meta-analysis" OR "systematic review" OR "cohort study"). Additional relevant articles were included at the authors' discretion.

Positive results should drive earlier and more routine integration of weight management into clinical care pathways to reduce disease severity, slow progression of multiple long-term conditions, and lessen societal burden. As newer weight-loss therapies expand and costs fall, broader application will become increasingly feasible, provided their benefits continue to outweigh harms and provided that trials and access extend to low-income and middle-income countries.

Contributors

All authors contributed to literature search, data interpretation, and writing (reviewing and editing). All authors read and approved the final version of the manuscript and accept responsibility to submit for publication.

Declaration of interests

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Supplementary appendix

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Supplementary appendix

From adiposity to multisystem morbidity: the case for weight loss as disease modification

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Table S1. A summary of key pieces of evidence from epidemiology, genetics and interventions (observational and limited RCTs) to support further testing of weight loss modalities in key CV conditions

	EPIDEMIOLOGY		GENETICS	INTERVENTIONS	
	Incident disease	**Prevalent disease**		**Observational data on weight loss**	**Randomised trials of weight loss and what further trials are needed**
Hypertension	In 16 312 476 non-hypertensive participants in Korea, higher baseline waist circumference was associated with incident hypertension; individuals in the highest category had a hazard ratio (HR) of 1·74 (95% CI 1·72-1·75) versus the reference group.[1] In a meta-analysis of 13 studies (n=125 329), both weight gain (RR 2·27; 95% CI 1·83-2·83) and persistent overweight (RR 3·29; 95% CI 2·18-5·28) from childhood to adolescence were associated with increased risk of hypertension in adulthood.[2] In The Johns Hopkins Precursors prospective cohort (n=1132 men; 46-year median follow-	In a pooled analysis of 837 population-based studies (n=7·5 million participants; 8 world regions), hypertension prevalence increased with BMI and waist-to-height ratio (WHtR). At BMI ⩾37·5 kg/m^2 and WHtR ⩾0·75, hypertension prevalence was ⩾39% in women and ⩾ 49% in men.[4]	A meta-analysis of 12 Mendelian randomisation studies (25 cohorts) suggested a causal association between BMI and hypertension: OR 1·10 (95% CI 1·08-1·13; 119 500 cases) per 1 kg/m^2 increment in BMI and OR 1·64 (1·47-1·82; 32 874 cases) per 5 kg/m^2 increment.[5] In 367 703 UK Biobank participants, genetically predicted BMI was associated with arterial hypertension (OR per genetically predicted 1 kg/m^2 increase in BMI 1·10, 95% CI 1·07-1·12, p=3·4×10^{-16}) with 119 500 cases. Additionally, OR per 1 kg/m^2 increase in fat mass index for arterial hypertension was 1·12, 95% CI 1·04-1·20, p=1·5×10^{-3}.[6]	In the MIRROR Slovakia Study (n=13 631 with a history of hypertension; 1-year follow-up), among those living with obesity, a BMI reduction ⩾1 kg/m^2 was associated with lower odds of uncontrolled hypertension (men OR 0·59, 0·48-0·71, p<0·0001; women OR 0·73, 0·61-0·88, p<0·001).[7] In the Framingham study, among adults living with overweight (BMI ⩾25 kg/m^2 (middle-aged 30-49 years; n=623 and older adults aged 50-65 years; n=605), weight loss ⩾6·8 kg after 4 years was associated with a 21-29% lower risk for long-term hypertension.[8] In a US Veterans retrospective cohort (5·1-year median follow-up; n=183 702 with BMI ⩾35	A meta-analysis of 25 randomised controlled trials (RCTs) (n=4874) showed that a 5·1 kg weight reduction (energy restriction, increased physical activity, or both) reduced SBP by -4·44 (-5·93 to -2·95) mmHg and DBP by -3·57 (-4·88 to -2·25) mmHg.[10] SBP and DBP reductions were approximately 1 mmHg per kg lost. In Diabetes Remission Clinical Trial (DiRECT) (n=143 intervention with total diet replacement), weight change was a significant predictor of change in blood pressure; SBP and DBP fell by 0·53 mmHg (95% CI 0·41, 0·65) and 0·34 mmHg (95% CI 0·26, 0·41), respectively, per kg of weight lost (p<0·0001 for both).[11] In SURMOUNT-1 (n=2539 with obesity or overweight), tirzepatide reduced SBP and DBP by 6·8 mmHg and 4·2 mmHg, respectively, versus placebo at 72 weeks; mediation analyses indicated that 68% of SBP

	up), obesity (body mass index (BMI) ⩾30 kg/m^2) in young adulthood was associated with incident hypertension (HR 4·17; 95% CI 2·34-7·42); overweight (BMI 25 to <30 kg/m^2) also associated with increased risk (HR 1·58; 95% CI 1·28-1·96).[3]			kg/m^2 and hypertension medically managed; n=3965 bariatric surgery), surgical management was associated with better blood pressure control, with average 5·4 mmHg (95% CI 4·9-5·9) lower systolic blood pressure (SBP) and 1·8 mmHg (95% CI 1·5-2·1) lower diastolic blood pressure (DBP).[9]	reduction and 71% of DBP reduction was estimated to be mediated by weight loss.[12] A meta-analysis of 85 RCTs (n=90 977; 8-month median follow-up) found glucagon-like peptide 1 receptor agonists reduced SBP by 3·4 mmHg (95% CI 2·8-4·0) and DBP by 0·9 mmHg (95% CI 0·5-1·2), with greater reductions observed for dual and triple agonists and with greater weight loss.[13] In a meta-analysis of 29 RCTs (n=2548), bariatric surgery produced larger blood pressure reductions (SBP -4·5 mmHg; 95% CI -7·0 to -2·0 and DBP -3·0 mmHg; 95% CI -4·8 to -1·3) than non-surgical strategies.[14]
Heart failure (HF)[15]	Associations of BMI with incident HF appear twice as strong as those for incident ASCVD. For example, among 1 610 437 Swedish male conscripts (mean age 18·6 years; median follow-up 23·0 years), those with a BMI of 35 kg/m² or more had a more than nine-fold greater risk of incident HF than those with a BMI of 18·5-20·0	Higher BMI associated with better outcomes (in line with apparent obesity paradox) BUT higher WHR associated with worse outcomes, suggesting body composition substantially altered in those with HF. The duration of severe obesity was associated with the prevalence of HF, with a prevalence of 70% and 90% after 20 and 30 years, respectively.[18–20]	Multiple studies show higher BMI SNPs predict incident HF. Among 367 703 UK Biobank participants, genetically predicted BMI was significantly positively associated with HF (OR per genetically predicted 1 kg/m^2 increase in BMI 1·12, 95% CI 1·07-1·16, p=$3·9\times10^{-7}$) with 4803 cases.[6] Additionally, OR per 1 kg/m^2 increase in fat mass index for HF was 1·22, 95% CI 1·06-1·41, p=$6·3\times10^{-3}$.[6]	From the Swedish National Patient Registry cohort including 47 859 patients with a primary diagnosis of obesity, the 22 295 who underwent bariatric surgery had a markedly lower risk of HF compared with people with obesity who did not have surgery (age- and sex-adjusted HR 0·37, 0·29-0·46) and the lower risk persisted after further adjustment for baseline differences in known risk	Several small trials of lifestyle induced weight loss suggest weight loss in HF is safe, and improves left ventricular mass, and exercise capacity.[24] Among 24 patients with congestive HF (of whom 14 were studied after weight loss) and 50 patients without HF (of whom 39 were studied after weight loss), substantial weight loss in those with and without congestive HF produced comparable reductions in mean LV internal dimension in diastole, LV end-systolic wall stress, LV mass/height index,

	kg/m² (HR 9·21, 95% CI 6·57-12·92).[16] In a meta-analysis including 647 388 participants, for a 5-unit increment in BMI the summary RR was 1·41, 1·34-1·47 for HF incidence.[17]		See also main text for information on BMI genes and outcomes in prevalent heart failure.	factors for HF (HR 0·37, 0·30-0·46).[21] In a meta-analysis including 8 cohort studies with 26 002 patients who had bariatric surgery and 40 657 controls, compared with controls, bariatric surgery was associated with a lower incidence of HF (HR 0·50, 95% CI 0·38-0·66, p<0·001).[22] In a study of 25 804 bariatric surgery patients from the Scandinavian Obesity Surgery Registry and 13 701 lifestyle modification patients from the Swedish nationwide registry, over a median of 4·1 years, surgery patients had a lower HF incidence than lifestyle modification (HR 0·54, 0·36-0·82).[23]	transmitral Doppler E-wave deceleration time, and left atrial dimension, and comparable increases in LV fractional shortening and transmitral Doppler E/A ratio.[20]
Heart failure with preserved ejection fraction (HFpEF)[25]	In the Framingham Heart Study including 6340 participants with 97 808 person-years of follow-up and 512 cases of incident HF, higher BMI was more strongly associated with risk of HFpEF than HFrEF.[26] In a pooled analysis from 3 large longitudinal cohort		See data above on HF in general.		In SECRET, among 100 patients with HFpEF, caloric restriction improved peak oxygen uptake, Kansas City Cardiomyopathy Questionnaire scores, and reduced bodyweight, left ventricular mass by MRI (-4g, 95% CI -7 to 0; p=0.03), and C-reactive protein.[24] In patients with obesity-related HFpEF, STEP-HFpEF (n=529) and STEP-HFpEF DM (n=616) showed that once-weekly semaglutide led to larger

	studies (WHI, MESA, CHS) including 51 451 participants with 3180 HF events, there was a graded association between higher BMI and risk of HFpEF. Compared with participants of a healthy BMI, those living with overweight and with class I obesity had a 38% and 56% higher risk, respectively, of HFpEF, independent of other risk factors. Lower BMI was more consistently associated with lower risk of HFpEF compared with HFrEF.[27]				reductions in heart failure-related symptoms and physical limitations and greater weight loss (-10·7 and -6·4 percentage points, respectively) than placebo at 1 year[28,29] In SUMMIT (n=731), tirzepatide led to a lower risk of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with HFpEF and obesity, and weight loss of 11·6%.[30] Two large cardiovascular outcome trials in patients with obesity and heart failure with preserved or mildly reduced ejection fraction are now recruiting: MARITIME-HF (maridebart cafraglutide; NCT07037459) and HF-POLARIS (zenagamtide, formerly amycretin; NCT07567001).
Heart failure with reduced ejection fraction (HFrEF)	See data above on HF in general.	See data above on HF in general.	See data above on HF in general.	In a non-randomised study of 37 stable idiopathic DCM (vs 23 matched controls), a diet intervention over 12 months was associated with a lower LVEDV by 8±10%, lower LVM by 6±9%, greater absolute LVEF by 8±6%.[31]	In 21 people with obesity and heart failure (LVEF ⩽40%), compared with diet counselling alone, orlistat improved 6MWT, functional class, weight loss and decreases in total cholesterol, LDL-C, triglycerides.[33] In a feasibility randomised study of 14 patients with HF (mean LVEF 27·8±7·1%), reduced body

				In a non-randomised prospective study, 32 individuals with obesity and dilated cardiomyopathy (baseline LVEF 40·8%) underwent CMR before and 12 months after a supervised dietary intervention. Among the 15 completers who lost weight (mean -8·1 kg), LVEF improved by 7·3 percentage points (39·5% to 46·8%; p=0·002) with reduced LV end-systolic volume, whereas no change was seen in those who gained weight. Change in LVEF correlated with change in body weight (r=-0·446, p=0·037).	weight and adiposity with high-protein diet improved functional status, lipid profiles, glycaemic control, QoL.[34] Larger scale trials of weight loss via dietary means and pharmacotherapy are clearly required. These should test the impact on KCCQ and, if possible, hard outcomes.
Coronary heart disease (CHD) / Coronary artery disease (CAD) / Angina	In the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), a pooled analysis of 97 prospective cohorts with 1·8 million participants found that the HR for each 5 kg/m² higher BMI was 1·27 (1·23-1·31) for CHD after adjustment for confounders, attenuating to 1·15 (1·12-1·18) after additional adjustment	BMI associations are less clear and sometimes reversed once coronary heart disease is established. In a collaborative analysis of individual data from 15 923 people with coronary artery disease (5696 deaths over a median 2·3 years), BMI was inversely associated with mortality (HR 0·64, 95% CI 0·59-0·69) whereas central obesity was directly associated with it (HR 1·70, 1·58-1·83), and central obesity remained predictive in those of a healthy BMI.[84]	Among 367 703 UK Biobank participants, genetically predicted BMI was significantly positively associated with coronary artery disease (OR per genetically predicted 1 kg/m^2 increase in BMI 1·07, 95% CI 1·04-1·10, p=$1{\cdot}3\times10^{-5}$) with 24 531 cases.[6] Additionally, OR per 1 kg/m^2 increase in fat mass index for coronary artery disease was 1·08, 95% CI 1·00-1·17, p=0·047.[6]	Large weight loss in bariatric surgery also associated with lower risk of incident ASCVD. In a meta-analysis including 7 cohort studies with 101 536 patients who had bariatric surgery and 322 551 controls, compared with controls, bariatric surgery was associated with a lower incidence of MI (HR 0·58, 95% CI 0·43-0·76, p<0·001).[22]	Ongoing trials with GLP-1RA which yield large weight loss (>10%) should add insights into independent benefits of weight loss. One such head-to-head trial with a GLP-1RA which causes modest weight loss, could be particularly revealing. Presently, it remains debated to what extent GLP-1RAs lower MACE via weight loss versus direct effects, with most evidence suggesting the main effect may be direct. See also the main text. In SELECT (n=17 604 with pre-existing cardiovascular disease

	for blood pressure, cholesterol, and glucose.[35]	Waist circumference and waist-to-hip ratio are more linearly related to cardiovascular risk than BMI, which shows a J-shaped association.[85]		Post hoc observational analysis from Look AHEAD including 4834 individuals, >10% weight loss over the first year was associated with 21% lower risk for incident events (HR 0·79, 0·64-0·98) (composite of CVD death, MI, stroke, or angina hospitalisation).[36]	and overweight or obesity but without diabetes), once-weekly subcutaneous semaglutide reduced non-fatal myocardial infarction vs placebo (HR 0·72; 95% CI 0·61-0·85); at 104 weeks, mean body weight change was -9·39% with semaglutide and -0·88% with placebo (estimated treatment difference -8·51 percentage points; 95% CI -8·75 to -8·27).[37] In SURPASS-CVOT, the dual GLP-1/GIP receptor agonist tirzepatide demonstrated cardiovascular benefit on MACE outcomes comparable to dulaglutide (a GLP-1RA with less weight loss but already shown to lessen MACE outcomes)[38] in patients with type 2 diabetes and established atherosclerotic cardiovascular disease.[39]
Microvascular angina	In 827 consecutive patients undergoing evaluation for coronary artery disease with cardiac stress positron emission tomography with median 5·6 years follow-up, coronary microvascular dysfunction (CMD) was independently associated with elevated BMI and adverse outcomes.[40]	Among 195 participants undergoing cardiac PET/CT, 42% had CMD and 84% were living with obesity. Nearly half of these symptomatic patients, most of whom were living with obesity, presented to the emergency department without evidence of MI or CAD and were found to have CMD.[42]		In 18 individuals living with severe obesity, weight loss via bariatric surgery was associated with improved endothelium-related myocardial blood flow responses to cold pressor test and hyperaemic myocardial blood flows.[43]	In a randomised trial enrolling 62 women with microvascular angina, a 24-week intervention comprising low energy diet, exercise training and intensified risk factor control resulted in significantly improved angina burden but no improvement of coronary microvascular function.[44] Patients in the intervention arm lost around 9 kg versus controls. In a small 8-week RCT, we reported metformin improved

	In 128 patients with non-obstructive CAD who underwent a PET scan, central obesity was associated with lower hyperaemic myocardial blood flow and myocardial flow reserve, and higher prevalence of CMD.[41]				vascular function and decrease myocardial ischaemia in non-diabetic women with chest pain and angiographically normal coronary arteries.[45] Further randomised trials of intentional weight loss over longer duration are clearly needed.
Atrial fibrillation (AF)[46,47]	In meta-analyses including 25 studies with 83 006 cases and 2 405 381 participants, a 5-unit BMI increment was associated with RR for AF of 1·28 (95% CI: 1·20–1·38).[48] In a meta-analysis of 626 603 individuals in 51 studies, every 5-unit increment in BMI confers ~30% greater risk of incident AF, 13% increase in recurrent AF post-ablation, and 10% increase in post-surgical AF.[49]	Limited data. Among the 9606 patients with AF analysed in the ORBIT-AF registry (10 135 enrolled), 78% were living with overweight or obesity: 23% had class I obesity, 12% class II, and 10% class III.[50] In the EORP-AF (EURObservational Research Programme AF) General Pilot Registry, among 2540 patients with AF, 29% were living with obesity.[51] In a Gulf SAFE registry including 1804 patients with AF, the prevalence of obesity was nearly one-third (31%).[52]	Among 367 703 UK Biobank participants, genetically predicted BMI was significantly positively associated with AF (OR per genetically predicted 1 kg/m^2 increase in BMI 1·07, 95% CI 1·04-1·09, p=3·6×10^{-7}) with 13 538 cases. Additionally, OR per 1 kg/m^2 increase in fat mass index for AF was 1·27, 95% CI 1·14-1·40, p=5·8×10^{-6}.[6]	Bariatric surgery associated with 41% lower risk for AF (HR, 0·59; CI, 0·44-0·78) in 5321 people with type 2 diabetes and obesity from a register-based nationwide cohort study in Sweden.[53] In the SOS (Swedish Obese Subjects) prospective matched cohort study in Sweden of 4021 individuals, weight loss through bariatric surgery reduced the risk of AF, with the risk reduction more apparent in younger people and in those with higher BP.[54] GOAL-AF, a single-arm feasibility study of liraglutide 3 mg before ablation for AF in people with a high BMI, has completed recruitment (29 enrolled against a planned 30) and remains active but unreported.[55]	In the context of treating diabetes, a meta-analysis of 31 randomised trials comprising ~18 000 patients with diabetes on GLP-1RA vs 15 000 controls concluded that GLP-1RAs did not influence AF incidence.[56] That noted, weight loss in such trials was modest, mostly <5%. In LOSE-AF, 118 people aged 60-85 years with a BMI of 27 kg/m² or more and persistent AF were randomised to an 8-month low-calorie diet with behavioural support or to usual care; the intervention produced greater weight reduction (9·7% vs 3·1%; estimated difference -6·9 kg, 95% CI -9·2 to -4·5) but did not improve AF symptom severity (between-group difference in Atrial Fibrillation Severity Scale score -0·9, 95% CI -3·3 to 1·4; p=0·43), AF burden, cardiac remodelling, or the need for further rhythm control intervention.[57]

					In a single-centre partially-blinded randomised controlled study in Adelaide, Australia, of 150 randomised to weight management or general lifestyle control, weight reduction (intervention group -14·3 kg vs -3·6 kg in controls) with intensive risk factor management resulted in reduction in AF symptom burden and severity and in beneficial cardiac remodelling.[58] SORT-AF included 133 patients randomised to weight-reduction versus usual care, showed that although the primary endpoint of AF burden after ablation did not differ between groups, effects of weight loss and improvement of exercise activity were beneficial.[59] Taken together, these trials suggest that weight loss of more than 10 kg may be needed before effects on AF become apparent. Future trials should therefore be powered around, and report outcomes by, the magnitude of weight loss achieved.
Stroke	For every 1 unit increase in BMI, the risk for ischaemic stroke was higher by ~5%.[60–63] In the Global Burden of Metabolic Risk Factors	Obesity is common after stroke: of 1937 participants with a recent ischaemic stroke or transient ischaemic attack allocated to placebo in the IRIS trial, 855 (44%) were living with obesity.[86]	Among 367703 UK Biobank participants, genetically predicted BMI was **not** significantly positively associated with ischemic stroke (OR per genetically predicted 1 kg/m2 increase in BMI 1·03, 95% CI 0·99-1·07,	In a meta-analysis including 9 cohort studies including 86601 patients who had bariatric surgery and 318599 controls, compared with controls, bariatric surgery was associated with a lower	In SELECT (n=17 604 with pre-existing cardiovascular disease and overweight or obesity but without diabetes), once-weekly subcutaneous semaglutide had no clear effect on non-fatal stroke vs placebo (HR 0·93; 95% CI 0·74-1·15); at 104 weeks, mean body

	for Chronic Diseases Collaboration (BMI Mediated Effects), a pooled analysis of 97 prospective cohorts with 1·8 million participants found that the HR for each 5 kg/m^2 higher BMI was 1·04 (1·01-1·08) for stroke after adjustment for confounders and with additional adjustment for 3 metabolic risk factors (blood pressure, cholesterol, glucose).[35] From a total of 33 cohort studies in the Asia-Pacific region involving 310 283 participants with 3332 stroke events, each 2 kg/m² lower BMI was associated with a 12%, 9-15% lower risk of ischaemic stroke, 8%, 4-12% lower risk in haemorrhagic stroke.[62] Compared with BMI, measures of central obesity are better predictors of stroke in most,[64–69] but not every study.[70]		p=0·20) with 3554 cases.[6] That noted, OR per 1 kg/m^2 increase in fat mass index for ischemic stroke was 1·38, 95% CI 1·19-1·60, p=2·2x10^{-5}.[6]	incidence of all strokes (HR 0·64, 95% CI 0·53-0·77, P<0·001).[22] In 3 cohort studies, the association of bariatric surgery with ischaemic stroke appeared more marked (HR 0·37, 95% CI 0·17-0·82, P=0·01). In a Swedish nationwide matched cohort restricted to people with type 1 diabetes, 387 individuals who had undergone Roux-en-Y gastric bypass were compared with 387 matched controls, with hospitalisation data followed for up to 9 years.[71] The findings suggested a lower risk in the surgery group for CV disease (HR 0·43; 0·20-0·90), CV death (HR 0·15; 0·03-0·68), hospitalisation for HF (HR 0·32; 0·15-0·67), and stroke (HR 0·18; 0·04-0·82).	weight change was -9·39% with semaglutide and -0·88% with placebo (estimated treatment difference -8·51 percentage points; 95% CI -8·75 to -8·27).[37] TOPS (Take Off Pounds After Stroke) randomised 38 patients after acute ischaemic stroke to a partial meal replacement programme or to enhanced standard care; weight loss of 5% or more at 12 weeks was achieved by 9 (53%) of 17 vs 2 (12%) of 17 (p=0·03), with no adverse events attributed to participation.[73] A randomised controlled trial of the SystemCHANGE™ weight management intervention in 61 adults with stroke or multiple sclerosis found no between-group difference in weight loss (p=0·18), although physical activity, depression, anxiety, and self-efficacy all improved with the intervention.[74]
Peripheral arterial	Obesity has been linked to higher risk for PAD. Obesity impairs	The relationship between BMI and outcomes is less clear in people with	Among 367 703 UK Biobank participants, genetically predicted BMI was	Limited and mixed data for association of bariatric surgery with incident	STRIDE randomised 792 people with type 2 diabetes and symptomatic peripheral artery

disease (PAD)[75]	functional burden and reduces time to claudication and lessens recovery from activity. Among 3 250 350 self-referred individuals at more than 20 000 US sites who were evaluated by screening ankle brachial indices for PAD, increasing BMI was a robust independent risk factor for PAD only in women.[76] In 13 988 ARIC participants followed up for a median of 24 years, higher BMI at baseline was associated with incident hospitalisation for PAD after adjusting for potential confounders, particularly its most severe form of critical limb ischaemia.[77]	established PAD and can show reverse patterns (the obesity paradox), with body fat distribution, sex, and sarcopenia among the proposed explanations.[75]	significantly positively associated with PAD (OR per genetically predicted 1 kg/m² increase in BMI 1·07, 95% CI 1·03-1·12) with 3514 cases. Additionally, OR per 1 kg/m^2 increase in fat mass index for PAD was 1·21, 95% CI 1·05-1·39, p=9·5×10^{-3}.[6]	PAD. People with intentional weight loss appear to have less functional decline versus those who put on weight. Among 389 patients with PAD, compared with weight gain, intentional weight loss was associated with less annual decline in 6MWD.[78]	disease to semaglutide or placebo for 52 weeks. The estimated median ratio to baseline in maximum walking distance at week 52 was greater with semaglutide than placebo (1·21 [IQR 0·95-1·55] vs 1·08 [0·86-1·36]; estimated treatment ratio 1·13, 95% CI 1·06-1·21; p=0·0004).[79]
Aortic stenosis	In Swedish cohorts of 71 817 men and women who were free of CVD and followed for a mean of 15·3 years, participants living with overweight and with obesity had a HR of 1·24 (1·05-1·48)		Among 367 703 UK Biobank participants, genetically predicted BMI was significantly positively associated with aortic stenosis (OR per genetically predicted 1 kg/m^2 increase in BMI 1·13, 95% CI 1·05-1·21, p=1·2×10^{-3}) with 1252 cases.		

	and 1·81 (1·47-2·23) respectively for incident aortic valve stenosis. The highest risk of aortic valve stenosis was present in individuals with obesity and substantially increased WC. In 7494 Swedish men followed up for a maximum of 42·8 years, higher BMI was associated with aortic stenosis.[81] In 798 Swedish men from the general population, BMI (OR per unit increase 1·23 (95% CI 1·10-1·38), p=0·0003) were significantly associated with increased risk of developing aortic sclerosis or aortic stenosis.[82]		Additionally, OR per 1 kg/m^2 increase in fat mass index for aortic stenosis was 1·46, 95% CI 1·13-1·88, p=3·9×10^{-3}.[6] Among 108 211 individuals from the Copenhagen General Population Study, a 1 kg/m^2 increase in BMI was associated with causal risk ratios for aortic valve stenosis of 1·52 (95% CI 1·23-1·87) genetically, with corresponding HR of 1·06 (95% CI 1·05-1·08) observationally.[83]		

Table S1 References

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Table S2. A summary of key pieces of evidence from epidemiology, genetics and interventions (observational and limited RCTs) to support further testing of weight loss modalities in key rheumatic, musculoskeletal, and dermatological conditions

	EPIDEMIOLOGY		GENETICS	INTERVENTIONS	
	Incident disease	**Prevalent disease**		**Observational data on weight loss**	**Randomised trials on weight loss**
Psoriatic arthritis (PsA)	Obesity is associated with increased risk of developing PsA. In a study of the UK general population, individuals with psoriasis and a BMI ⩾35 kg/m² had a 48% higher risk of developing PsA than individuals with psoriasis and a BMI <25 kg/m², after adjustment for conventional risk factors[1]. In a secondary analysis of all individuals, regardless of psoriasis status, having a BMI ⩾35 kg/m² almost doubled the chance of an individual having PsA compared with individuals with a BMI <25 kg/m².[1] In a separate study of US women, BMI ⩾30 was associated with 3x the risk of PsA, and BMI >35, over 6x the risk (vs BMI <25).[2]	The prevalence of obesity is increased in PsA. This varies by study and population, but estimates are that 28% to 45% of individuals with PsA are living with obesity.[3,4] In a study of over 500 000 individuals from the UK Biobank, the average BMI in PsA was 28·6 in men and 28·9 in women, compared with 27·8 and 27·1 kg/m² in controls respectively.[5] PsA is also associated with a metabolically adverse body composition profile with greater visceral adipose tissue and liver fat percentage than age, sex and BMI matched controls, which is associated with increased propensity to type 2 diabetes and CHD.[6] **Disease severity:** Obesity is associated with worse disease activity. BMI >30 is associated with a 47% decreased odds of achieving minimal disease activity (compared with BMI <25).[7]	A Mendelian randomisation (MR) study using data from the UK Biobank has shown that genetically predicted BMI is associated with increased risk of PsA (OR 1·38 per 4·8 kg/m² increase in BMI; 95% CI 1·14, 1·67) and psoriasis (OR 1·36; 95% CI 1·18, 1·58). In contrast, the reverse ie genetic liability to PsA or psoriasis did not predict BMI.[10] Another MR study assessed the effect of genetic variants associated with childhood and adult body sizes on risk of developing PsA. This showed that both child and adult body size predicted development of PsA (OR 2·18, (95% CI 1·43, 3·31) and 1·64	Data in this area is limited but promising. One small study of 46 patients suggested weight loss is associated with improved disease activity. 12-16 weeks of a very low-calorie diet (640 kcal) in patients with PsA and obesity resulted in a median 18·7 kg weight loss after 6 months and an increase from 29% to 54% in the proportion of patients with PsA achieving minimal disease activity (MDA).[12] There was however no control group for comparison.	One randomised study has suggested weight loss is associated with improved response to TNF-I therapy. 138 individuals with PsA and overweight or obesity starting TNF-inhibitors were randomised to a hypocaloric diet or free managed diet. Irrespective of diet, those who lost ⩾5% and >10% body weight were over 4x and 6x as likely to achieve MDA compared with <5% weight loss.[13] This study offers promise for weight loss in treatment of PsA but lacks formal clinical trial registration and adherence to RCT standards. The TOGETHER-PsA trial is discussed in the main paper.

		Response to treatment: Obesity diminishes response and adherence to TNF-Is in PsA.[8,9]	(95%CI 1·18, 2·29) respectively).[11]		
Psoriasis	Obesity is associated with increased risk of developing psoriasis. A study of 33 734 people in the population-based Nord-Trøndelag Health Study (HUNT) identified 369 incident psoriasis cases. A 1 SD higher BMI and waist circumference was associated with a 22% to 26% increased risk of developing psoriasis. Obesity was associated with an 87% increased risk of new onset psoriasis vs those with healthy weight (RR 1·87 (95% CI 1·38, 2·52)). Those whose body weight increased by ⩾10 kg were also at significant increased risk of developing psoriasis (RR of 1·72 (95% CI 1·15-2·58) vs those with a stable weight.[14]	Individuals with psoriasis are more likely to be living with obesity. A systematic review and meta-analysis of 16 observational studies with 2·1 million individuals revealed that individuals with psoriasis have a 66% greater odds of obesity vs those without psoriasis (pooled OR 1·66 (95% CI 1·46–1·89)). Further, the odds of obesity increase with increasing psoriasis severity, with those with severe psoriasis having over double the odds of obesity (pooled OR 2·23, 95% CI 1·63-3·05).[15] **Response to treatment:** Obesity is also associated with poorer response to treatment. In a study of over 2000 people with psoriasis who were started on a new systemic treatment (including conventional DMARDs, PUVA, or biologics), the response to treatment fell with increasing BMI. The odds of	Mendelian randomisation (MR) has shown that higher BMI causally increases the odds of psoriasis by 9% per 1 unit increase in BMI (OR 1·09, [95% CI 1·06–1·12]). In contrast, MR estimates gave little support to a possible causal effect of psoriasis genetic risk on BMI.[18] A systematic review of 5 MR studies investigated the relationship of BMI with psoriasis. BMI was found to be causally associated with psoriasis in all 5 studies with an OR ranging from 1·09 to 1·59.[19] Another MR study showed the site of fat storage may be important in psoriasis onset. Genetic variants associated	Two studies of patients undergoing bariatric surgery have suggested that weight loss may reduce the risk of developing psoriasis. A large population-based cohort study in Denmark of 12 364 and 1071 patients receiving gastric bypass or gastric banding respectively, showed gastric bypass was associated with a significantly reduced risk of almost half in developing new onset psoriasis (adjusted HR 0·52 (95% CI, 0·33-0·81)) and reduced progression to severe psoriasis (adj. HR 0·44 (95% CI, 0·23-0·86)). There was no such effect with gastric banding.[21] A separate study of 1991 people who underwent bariatric surgery and 2018 controls with obesity from the Swedish Obese Subjects (SOS) Study showed bariatric surgery was associated with a mean decrease in BMI of -17% after 10 years (vs +1·7% in controls). Bariatric surgery was associated with a 35%	A meta-analysis of 6 RCTs showed weight loss following lifestyle interventions (diet or physical activity) decreased psoriasis severity compared with controls. Interventions lasted from 12 to 24 weeks with weight loss ranging from -3·0% to -14·8% body weight. Collectively, lifestyle interventions resulted in an almost 50% greater chance of achieving a ⩾75% improvement in Psoriasis Area and Severity Index (PASI) (RR 1·47, [95% CI 1·27, 1·69]), and an average mean decrease in PASI score of -2·59 [95% CI -4·09, -1·09].[23] One small RCT of 20 patients with plaque psoriasis and obesity (without diabetes)

		achieving a 75% improvement in PASI (PASI75) after 16 weeks treatment fell by 38% in those with obesity (OR 0·62 (95% CI, 0·49–0·79)) vs healthy weight.[16] Obesity is associated with a lower response to TNF-inhibitors and IL-17 inhibitors in psoriasis. Analysis of individuals in the Corrona Psoriasis Registry revealed obesity reduced the odds of achieving PASI75 by 25% (OR 0·75, 95% CI 0·64-0·88) and PASI90 by 30% (OR 0·70, 95% CI 0·59-0·81).[17]	with 'unfavourable adiposity' ie a fat distribution in subcutaneous and visceral adipose tissue as well as ectopic liver and pancreatic fat, were associated with over double the odds of developing psoriasis (OR 2·11, 95% CI 1·49, 2·99).[20]	reduction in risk of developing psoriasis vs controls receiving non-surgical treatment (HR 0·65; 95% CI: 0·47-0·89).[22]	treated with daily liraglutide showed a reduction in body weight of 4·7 kg vs 1·6 kg in those given placebo for 8 weeks. However, there was no significant change in PASI, DLQI, or hsCRP.[24] This may relate to a relatively mild degree of weight loss, short follow-up, and small sample size. The TOGETHER-PsO trial is discussed in the main paper.
Rheumatoid arthritis (RA)	Three large meta-analyses have shown that overweight and obesity are associated with increased risk of RA.[25–27] These include a meta-analysis of 16 studies with a total of 406 584 participants which found that overweight and obesity were associated with a 12% and 23% increased risk of developing RA respectively compared with healthy weight (pooled RR 1·12 (95% CI, 1·04-1·20) and 1·23 (95% CI, 1·09-1·39)). A dose-response meta-analysis revealed that each 5 kg/m² increase in BMI resulted in an 8% increase in risk of RA.[27]	The prevalence of overweight and obesity in RA varies by region. A worldwide study identified 18% of patients with RA as living with obesity,[28] while a UK-based study found 68% of patients were living with overweight and 31% with obesity.[29] **Response to treatment:** Obesity is also associated with reduced therapeutic response and low remission rates in RA.[30,31]	Genetic studies are consistent with epidemiological evidence that increased BMI increases the risk of RA. In a large MR study, genetic data from more than 850 000 individuals of European ancestry showed the risk of RA increased by 22% for a one SD (4·8 kg/m²) increment in genetically predicted BMI (OR 1·22 [95% CI 1·09–1·37]). This	Observational studies suggest weight loss can reduce RA disease activity, although these are limited in their small sample sizes, retrospective nature, and lack of control groups. A retrospective study of 53 patients with RA (average BMI 47·8 kg/m²) who underwent bariatric surgery showed after 12 months, an average weight loss of 41·0 ± 17·3 kg with a reduction in the proportion of patients with moderate to high disease activity, reducing from 57% at	There is one small proof of concept randomised trial assessing the effect of weight loss on disease activity in RA. 40 study participants with RA and a BMI of 30 kg/m² or more were randomised to either a hypocaloric diet of 1000-1500 kcal/day (n=20) or a control group. After 12 weeks, the diet intervention group lost an average of 9·5

			risk was comparable between men and women.[32] A separate MR study of data from the UK Biobank confirmed this association. A one SD higher genetically predicted BMI increased the incidence rate for RA by 52% (IRR=1·52; 95% CI=1·36-1·69).[33]	baseline to 6% after 12 months. After almost 6 years of follow-up, 74% of patients were in remission.[34] In a separate retrospective cohort study of 174 patients with RA seen at routine clinic visits and followed for almost 2 years, patients living with overweight or obesity who lost ⩾5 kg had three times increased odds of disease activity improvement (as measured by CDAI (clinical disease activity index) decrease of ⩾5) vs those who did not lose weight (OR 3·03, 95% CI 1·18–7·83).[35] However, given the retrospective study design, it is possible the converse may be true ie those with improved disease activity may be more likely to lose weight through less pain and increased physical activity. Finally, a further small study of 16 patients (10 with RA and 6 with PsA) with a BMI >30 kg/m^2 were identified from retrospective review of electronic medical records. These patients had been shown to have achieved a ⩾ 10% weight loss from either non-surgical or gastric bypass	kg per patient vs 0·5 kg in the control group. 72·2% of patients in the intervention group lost ⩾5% of baseline body weight vs 10·5% in the control group. Patient reported outcomes eg RAPID3 improved significantly between groups in favour of the dietary intervention; DAS28 and HAQ-DI improved significantly within the diet group, although the study was likely underpowered to detect significant differences between intervention and control groups.[37]

				surgery. On follow-up, median DAS28 scores decreased by 0·9, with an increase in the percentage of patients achieving remission (from 6% to 63%) with the majority not requiring intensification of medical treatment. However, again the numbers were small and there was no information on change in disease activity in those that did not lose weight.[36]	
Gout	Obesity is associated with increased incidence of gout. Analysis of the THIN database, covering over 1·7 million individuals and 24 768 newly diagnosed cases of gout, showed that those with a BMI between 25–29 kg/m² had a multivariate OR of 1·62 (95% CI 1·55, 1·70) for incident gout and those with BMI of ⩾30 kg/m² an OR of 2·34 (95% CI 2·22, 2·47) vs those with a BMI 20–24 kg/m².[38] Such a dose dependent relationship between BMI and incident gout was also seen in the Framingham Heart Study. Out of 2476 women and 1951 men, 304 developed gout (104 of them among women). Compared with BMI <25 kg/m^2, women with a BMI of 25-29·9 and ⩾30 kg/m^2 had multivariate RR of incident gout of 1·44 (95% CI 0·88–2·37) and 2·74 (1·65–4·58) respectively. In men, the multivariate RR was 1·76 (1·22–2·54) and 2·90 (1·89–4·44) respectively.[39] In the Health Professionals Follow-up Study (HPFS), 47 150 men with no gout at baseline were followed up for 12 years with 730 incident gout cases. Again, compared with those with BMI of 21 to 22·9 kg/m^2, the multivariate RR of gout was 1·95 (95% CI 1·44-2·65) with BMI of 25 – 29·9 kg/m^2, 2·33 (95% CI, 1·62-3·36) for men with a BMI of 30 to 34·9 kg/m^2, and 2·97 (95% CI, 1·73-5·10) for men with a BMI of ⩾35 kg/m^2. Further, men that gained ⩾30 lb over follow-up were almost twice as likely to develop gout (RR 1·99,	Using data from the National Health and Nutrition Examination Survey, it is estimated that 53% of individuals with gout are living with obesity (compared with 33% of those without gout).[44]	Multiple studies show higher adiposity SNPs predict hyperuricaemia and gout. MR analysis of the Global Urate Genetics Consortium showed a one standard deviation (about 4·6 kg/m²) increase in genetically predicted BMI was associated with an odds ratio of gout of 2·24 (95% CI 1·70, 2·95) and with a 0·30 mg/dL (95% CI 0·25, 0·35) increase in serum urate concentrations.[45] In a separate study of 6184 participants in	While national guidelines recommend weight loss in gout management, the evidence for weight loss interventions to date is limited and of poor quality. In a systematic review of 10 suitable studies (one RCT, and 9 non-randomised studies), with interventions including diet with or without physical activity, bariatric surgery, diuretics, metformin, or no intervention, mean weight loss ranged from 3 to 34 kg. The change in serum uric acid ranged from -168 to 30 µmol/L, with 0-60% of patients achieving the serum urate target <360 µmol/L. 6/8 (75%) of studies showed beneficial effects on gout attacks. In the short-term (within one month), there was a temporary increase in serum	RCT data is limited and more studies are urgently needed. A proof-of-concept RCT randomised 61 participants to intensive weight loss with a 16-week hypocaloric total diet replacement and weekly dietitian visits (n=29) or to a control group receiving ordinary foods with a dietitian visit at baseline and week 8 (n=32). At 16 weeks both groups had lost weight, -15·4 kg with the intervention and -7·7 kg with control (between-group difference 7·7 kg, 95% CI 4·7-10·7). Serum urate fell by -

	95% CI, 1·49-2·66) compared with men who maintained steady weight. Similarly, men who lost ⩾10 lb were less likely to develop gout (multivariate RR 0·61, 95% CI, 0·40-0·92).[40] As such, weight change over time can predict the risk of future gout. A separate study of 6263 women without prior history of gout included in the Atherosclerosis Risk in Communities (ARIC) Study, identified 103 women with newly diagnosed gout over 9 years follow-up. Again, a graded relationship was seen between BMI and incident gout. Compared with those with a BMI <25 kg/m^2 at baseline, the adjusted RR of incident gout was 1·63 (95%CI 0·84, 3·18) with a BMI 25–29·9 kg/m², 2·76 (95%CI 1·40, 5·44) with a BMI 30–34·9 kg/m², and 3·90 (95%CI 1·95, 7·82) with a BMI ⩾35 kg/m².[41] Women with the highest tertile of weight gain (⩾16·3 kg) from age 25 years to baseline had twice the risk of incident gout vs individuals in the lowest tertile (multivariate RR 2·05; 95% CI 1·06, 3·96). To investigate association between weight change patterns across adulthood and incident gout, weight trajectories from over 11 000 individuals in the National Health and Nutrition Examination Survey (NHANES) was analysed, with 320 incident gout cases. This showed gaining weight was a significant risk factor for incident gout (HR 1·65; 1·19–2·29). Further, if individuals had maintained a healthy BMI, 32·9% (95% CI 18·2–44·9) of gout cases could have been prevented for 10 years.[42] Obesity also increases the risk of recurrent gout attacks. Analysis of 11 816 people free of gout at baseline in the Multiple Risk Factor Intervention Trial, revealed 408 incident gout cases, with 132 developing recurrent gout attacks over 7-year period. Compared with individuals with no BMI change, the risk of recurrent acute attacks increased as BMI change increased (adjusted OR 1·60 (0·89–2·89) for a >5% increase in BMI), and decreased with a fall in BMI >5% (adjusted OR 0·61 (0·32–1·16)).[43]		the CoLaus study, a bidirectional Mendelian randomisation approach showed genetically predicted serum urate levels were not associated with fat mass, whereas genetic variants of fat mass (FTO, MC4R, TMEM18) were positively associated with serum uric acid levels. This suggests elevated serum uric acid is a consequence rather than a cause of obesity.[46] A large study of data drawn from more than 10 consortiums with 1 416 157 individuals showed a 1-SD increase in body fat mass (BFM) was associated with increased urate (0·24 (0·16 to 0·33, p<0·001), and 62% higher odds of gout (OR 1·62, 95% CI 1·02-2·57).[47]	urate and gout attacks with bariatric surgery. The review concluded available evidence is in favour of weight loss for individuals with overweight or obesity and gout, but is of low quality.[48]	0·6 mg/dL and -0·3 mg/dL respectively, but the between-group difference was not significant (-0·3 mg/dL, 95% CI -0·9 to 0·3; p=0·74), and differences in fatigue and pain were likewise not confirmed.[49]

Table S2 References

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Table S3. A summary of key pieces of evidence from epidemiology, genetics and interventions (observational and limited RCTs) to support further testing of weight loss modalities in key respiratory conditions

	EPIDEMIOLOGY		GENETICS	INTERVENTIONS	
	Incident disease	**Prevalent disease**		**Observational data on weight loss**	**Randomised trials on weight loss**
Asthma	Observational studies show an association between increased BMI and greater risk of developing asthma.[1–3] A large meta-analysis of 7 studies with 333 102 participants showed that those with a BMI of 25 kg/m² or more had 51% greater odds of incident asthma than those of a healthy weight (OR 1·51, 95% CI 1·27-1·80). The odds increased with increasing BMI.[1]	Obesity is associated with greater prevalence of asthma,[4] poorer asthma control[5] including less steroid responsiveness,[6] increased morbidity, and poorer quality of life.[7] In the 2016 wave of the West Sweden Asthma Study, a cross-sectional survey of 24 534 individuals aged 16-75 years, those with a BMI of more than 30 kg/m² had over double the odds of asthma compared with the study's reference category of BMI less than 18·5 kg/m² (OR 2·60, 95% CI 1·63-4·13 for current asthma; and OR 2·50, 95% CI 1·61-3·88 for physician diagnosed asthma).[4] Obesity is associated with poorer response to glucocorticoids in asthma with a blunted in vitro response to dexamethasone.[6] Individuals with asthma and obesity were more likely to report continuous symptoms (OR 1·66, 95% CI 1·09 to 2·54), miss more work days (OR 1·35, 95% CI 1·01 to 1·81), and use controller medication (OR 1·37, 95% CI 1·01 to 1·85), compared with those with BMI <25. People with obesity were also less	Genetic studies have shown a causal association of BMI with increased asthma risk.[8–10] Mendelian randomisation of 56 105 adults in the Norwegian Nord-Trøndelag Health Study (HUNT) demonstrated OR 1·36 (95% CI 1·10–1·68), 1·49 (95% CI 1·14–1·94) and 1·40 (1·02–1·93) per 4·1 kg/m² BMI increase and "ever asthma," doctor-diagnosed asthma, and doctor-diagnosed active asthma respectively. There was no clear association between genetically predicted asthma and adiposity markers.[8]	Data on weight loss strategies in managing asthma with obesity suggest bariatric surgery may be associated with reduction in both systemic and airway pro-inflammatory markers,[11] improvement in lung function,[12] asthma control, quality of life scores, and a reduction in treatment burden.[13,14] Preliminary evidence also suggests asthma control may improve and, in some individuals, that remission may occur,[15,16] but this requires further study to confirm. Studies in this area are mainly observational, in a small number of individuals, and with open-label study design.	An original Cochrane review in 2012 of 4 studies with 197 adults with asthma suggested weight loss may improve asthma control, but the evidence based was of poor quality.[17] Following this, there have been several randomised trials to investigate dietary and other lifestyle approaches to weight loss and asthma outcomes. In a randomised trial of 330 adults with obesity and uncontrolled asthma, there was no significant change in Asthma Control Questionnaire (ACQ) score or quality of life with a lifestyle intervention (calorie reduction, moderate intensity physical activity, and behavioural self-management skills) compared with standard care. However mean

		likely to be in asthma remission (OR 0·56, 95% CI 0·38 to 0·82).[7]			weight loss with the intervention was modest (-4 kg).[18] A smaller trial of 46 participants with obesity and asthma randomised to either a 10-week dietary, exercise, or combined dietary and exercise intervention, showed mean weight loss of 8·5%, 1·8% and 8·3% respectively. Asthma control improved after dietary and combined interventions, and quality of life improved after all interventions. This study suggested a weight-loss goal of 5–10% to assist in the clinical management of adults with asthma and overweight or obesity.[19] In a randomised controlled trial of 55 individuals with obesity and well controlled asthma, randomised to either a nutrition and 10-week weight loss diet programme (intervention) or standard care (control group), those in the dietary group lost a mean of 5·2 kg body weight with improved asthma

					control and quality-of-life scores.[20] A randomised controlled feasibility trial of 35 participants with difficult-to-treat asthma and a BMI of 30 kg/m² or more, randomised to either the Counterweight-Plus (CWP) programme (12 weeks of total diet replacement at 800 kcal/day) followed by food reintroduction and weight loss maintenance, or usual care, showed after 16 weeks, those in the CWP group lost an average of 13·5 kg (compared with 1·4 kg in controls) with clinically significant improvements in asthma control and quality of life.[21]
Chronic obstructive pulmonary disease (COPD)	Observational studies are conflicting in the relationship of BMI with incident COPD. Studies have shown underweight (BMI <18·5 kg/m²) has been associated with increased risk of COPD[22,23,] and those with overweight or obesity (defined by BMI) with reduced risk of COPD.[24]	The prevalence of COPD rises steadily with BMI. Among 113 622 lifelong non-smokers aged 50 years and over in the 2012 US Behavioral Risk Factor Surveillance System, COPD prevalence rose from 2·5% in men and 3·5% in women of a healthy weight (BMI <25 kg/m²) to 7·6% in men and 13·4% in women with a BMI of 40 kg/m² or more; after adjustment for seven potential confounders, the odds of COPD with class III obesity were 3·21-fold higher in men (95% CI 2·46-4·20) and 4·00-fold	Genetic studies have suggested a causal association of BMI with increased COPD risk and mortality.[31–34] A meta-analysis of two Mendelian randomisation (MR) studies revealed genetically predicted higher BMI was associated with increased risk of COPD (OR 1·65 (95% CI 1·47–1·85)).[31]	There are few clinical studies investigating weight loss in COPD. In a small proof-of-concept study, 28 participants with COPD and obesity (BMI ⩾30 kg/m²) received a 12-week weight reduction programme involving low energy diet with meal replacements, dietary counselling, and resistance exercise training. Mean BMI	The INSIGHT COPD clinical trial set out to investigate whether targeted weight loss improved clinical outcomes in COPD. 684 participants with a mean BMI of 33·0 kg/m² and moderate COPD were randomised for 12 months to usual care or usual care plus lifestyle intervention consisting of a self-directed video

	However, when assessing the relationship between waist circumference, a more accurate marker of adiposity, in particular central adiposity, there is a direct relationship between increasing waist circumference and incidence of COPD, with women with a waist circumference of 110 cm or more and men 118 cm or more associated with a 76% greater risk of COPD (adj HR 1·76, 95% CI 1·48-2·08) (adjusted for age and sex).[25] This suggests greater central adiposity with greater visceral fat may play a role in development of COPD. Further, the positive association of underweight assessed by BMI with greater COPD incidence may reflect low muscularity and confounding by existing comorbidities, as BMI is particularly susceptible to reverse causation and confounding by pre-existing disease.[26]	higher in women (3·52-4·55) than in those of a healthy weight.[27] Overweight and obesity are prevalent among people with COPD. In an American study of 364 veterans with COPD, almost 70% were living with overweight or obesity.[28] Those living with overweight or obesity reported increased dyspnoea, poorer health related quality of life, and were prescribed more inhaled medications than those with healthy weight.[28] Data shows increasing severity of obesity is independently associated with worse respiratory-specific and general quality of life, reduced 6 minute walk test, increased dyspnoea, and greater odds of severe acute COPD exacerbations.[29] Data has suggested an "obesity paradox" in COPD with reduced mortality in those who are overweight (BMI 25-<30) (HR 0·62) or with obesity class I (BMI 30-<35) (HR 0·75) and increased mortality in underweight. However, those with more significant obesity (BMI >40 kg/m²) have shown greater mortality. It is possible however that this obesity paradox may relate to residual confounding and reverse causality where lower BMI may be reflective of unintentional weight loss from unmeasured coexisting comorbidities increasing mortality risk.[30]	In a separate analysis, genetic risk scores associated with obesity (BMI and waist:hip ratio) associated with increased risk of COPD, with a stronger association of WHR with COPD in men (OR 1·89, 95% 1·62, 2·19) than women (OR 1·22, 95% 1·10, 1·36). This association was partially attenuated after accounting for smoking status, suggesting smoking may lie on the causal pathway between obesity and lung disease.[34]	was 36·3 kg/m² at baseline and fell by 2·4 kg/m² (SD 1·1) after the intervention. Clinical outcomes including exercise capacity, health status, dyspnoea, strength and functional outcomes, improved with weight loss. Skeletal mass was preserved. This study was limited by small sample size and lack of control group.[35]	programme delivering the Diabetes Prevention Program's Lifestyle Balance curriculum, a low intensity programme to promote modest weight loss and moderate intensity physical activity. After 12 months, those randomised to the intervention arm walked further, had less breathlessness at the end of the 6-minute walk test, and had greater weight loss (adjusted difference -1·34 kg) than controls. However, the intervention did not improve the odds of achieving clinically meaningful improvements in walking distance or breathlessness. This may have related to the modest amount of weight loss (average 2·7 kg) with the intervention.[36] There was no evidence of harm from the intervention.

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Table S4. A summary of key pieces of evidence from epidemiology, genetics, and interventions (observational and limited RCTs) to support further testing of weight loss modalities in key gastrointestinal and hepatic conditions

	EPIDEMIOLOGY		GENETICS	INTERVENTIONS	
	Incident disease	**Prevalent disease**		**Observational data on weight loss**	**Randomised trials of weight loss**
Gastro-oesophageal reflux disease (GORD)	From a meta-analysis of 42 observational studies including 11 cohort studies, abdominal obesity was associated with reflux oesophagitis with aOR 1·51 (1·37-1·66, p<0·001) and pooled SMD 0·36 (0·30-0·42, p<0·001).[1] From UK Biobank (n=451 097) observational associations, higher odds of GORD were noted for a 1 SD higher BMI OR 1·28 (1·27-1·29), WHR OR 1·43 (1·41-1·46), WC OR 1·33 (1·31-1·36) and body-fat percentage OR 1·53 (1·50-1·55) – using MR, strong evidence that higher WHR and higher WHR adjusted for BMI lead to GORD, but weak evidence that higher BMI, body-fat percentage caused GORD. The MR-estimated effect for WHR equates to 1·23-fold higher odds of GORD per 5-cm increase in WC.[2]	Prevalence of GORD symptoms is high (37%) in people living with overweight or obesity.[4]	From large-scale GWAS and summary-level data from UK Biobank, the FinnGen study and large consortia of European ancestry, genetically predicted higher adulthood BMI (n=806 834) was associated with an increased risk of GORD – for each 1 kg/m² of genetically predicted adulthood BMI, OR 1·27 (1·21-1·33), $p=2·65\times10^{-25}$. Corresponding values for each 1-SD increase in genetically predicted adulthood waist-hip ratio (WHR) (n=697 734) OR 1·31 (1·23-1·41), $p=3·67\times10^{-15}$.[5] From genome-wide association meta-analysis of 71 522 GORD cases and 261 079 controls of European descent from UK Biobank and QSkin Sun and Health studies, OR of GORD was 1·49	Data of 1659 patients referred for assessment of GORD symptoms (24-h pH monitoring off medication and oesophageal manometry) between 1998-2008 were analysed and showed compared with patients of a healthy weight, those with obesity were more likely to have a mechanically defective lower oesophageal sphincter OR 2·12 (1·63-2·75).[7] In 332 adults prospectively enrolled, following a structured weight loss programme (dietary modifications, increased physical activity, behavioural changes) with an average weight loss of 13±7·7 kg achieved at 6 months compared with baseline, there was a decrease in the prevalence of GORD (15 vs 37%; p<0·01) and in the mean GORD symptom score (1·8 vs 5·5; p<0·01). Overall, 81% had a reduction in GORD symptom scores; 65% had complete resolution, and 15% had partial resolution of reflux symptoms. There was a significant correlation between % body weight loss and reduction in	In 2 RCTs, weight loss was followed by decreased time with oesophageal acid exposure.[8] In an RCT of 98 veterans with symptomatic GORD, modification of dietary carbohydrate intake improved symptoms of GORD.[9] In a small RCT, dietary weight loss intervention (individualised low-calorie diet programme) for 6 months produced weight loss and improved GORD symptoms (n=31) compared with control group (n=31).[10] In a single-centre RCT of 109 patients with type 2 diabetes scheduled for bariatric surgery, at 3 years, compared with sleeve gastrectomy, gastric bypass was associated with less reflux symptoms (between-group difference 0·54, 0·17 to 0·90) and greater total

	From a meta-analysis of 8 studies, aOR for GORD symptoms 1·43 (1·158-1·774) for BMI 25-30, 1·94 (1·468-2·566) for BMI >30.[3]		(1·40-1·60) for 1 SD increase in BMI.[6]	GORD symptom scores (r=0·17; p<0·05).[4]	bodyweight loss (8% difference, 25% vs 17%).[11] SLEEVEPASS was an RCT comparing laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y-gastric bypass (LRYGB) in 240 patients in Finland, which studied the effect on reflux. At 10 years, % excess weight loss was greater after LRYGB and the procedures were not equivalent for weight loss, but both LSG and LRYGB resulted in good and sustainable weight loss. Oesophagitis was more prevalent after LSG, but the cumulative incidence of Barrett's oesophagus was markedly lower than in previous trials and similar after both procedures.[12]
Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH)	From two prospective studies (Humedica n=1 048 934 and THIN n=1 133 525), using BMI of 20-22·5 kg/m^2 as the reference category, the risk of recorded NAFLD/NASH increased linearly with BMI and was approximately 5-fold higher in Humedica and 9-fold higher in THIN at a BMI of 30-32·5 kg/m^2 rising to around 10-fold higher in Humedica and	From a systematic review and meta-analysis of 151 studies comprising 101 028 individuals, the prevalence of NAFLD in the overweight population was 69·99%, the prevalence of NAFL was 42·49%, and the prevalence of NASH was 33·50%. Similar prevalence estimates were reported in the population with obesity	Lifelong, genetically driven NAFLD causally promotes T2D with a late-onset type 1-like diabetic subphenotype and central obesity; while genetically driven T2D, obesity, and central obesity all causally increase the risk of NAFLD.[16] A cross-tissue omics analysis discovers 10 adipose genes encoding secreted proteins that may	From a meta-analysis of single-arm, non-randomised comparative, or randomised trials of weight loss interventions which included 43 studies (26 behavioural weight loss programmes, 9 pharmacotherapy, 8 surgery) with 2809 participants with a median follow-up of 6 months, every 1 kg of weight loss was associated with a 0·83-unit reduction in ALT, a 0·56-unit reduction in AST, and a 0·77 percentage point reduction in	In the BRAVES multicentre, open-label, randomised trial of 288 randomised participants, bariatric-metabolic surgery was found to be more effective than lifestyle intervention in the treatment of NASH; primary endpoint of histological resolution of NASH without worsening of fibrosis at 1 year follow-up.[25] From a meta-analysis of 22 RCTs of weight loss

	14-fold higher in THIN in the 37·5 to 40 kg/m² BMI category.[13]	for NAFLD (75·27%), NAFL (43·05%) and NASH (33·67%).[14] The prevalence of NAFLD is 15-30% of the general population and close to 50-90% in people with obesity. Hepatic steatosis is found in 65% of people with class I-II obesity (BMI 30-39·9 kg/m^2) and in 85% of those with class III obesity (BMI 40-59 kg/m^2).[15]	modulate NAFLD pathogenesis by impacting adipose tissue function. Genetically regulated adipose expression of the NAFLD differentially expressed genes may contribute to NAFLD through changes in serum triglyceride levels.[17] Genetic variants associated with predisposition toward development and/or progression of NAFLD include PNPLA3, TM6SF2, GCKR, MBOAT7, HSD17B13, IGFBP2, PGC1alpha, SIRT1, miR-122, and miR-34.[18] Additionally, also PPP1R3B, IRGM, LPIN1.[19]	steatosis (assessed by radiology or histology).[20] From a meta-analysis of randomised and clinical controlled trials with 3037 participants with NAFLD, there was a dose-response relationship between degree of calorie restriction and beneficial effects on liver function and weight loss.[21] From a meta-analysis of 32 cohort studies comprising 3093 biopsy specimens, bariatric surgery resulted in biopsy-confirmed resolution of NAFLD and improvement of the NAFLD Activity Score in a substantial proportion of patients.[22] From a meta-analysis of 3 RCTs and 4 single-arm trials including 330 patients with NAFLD or NASH investigating orlistat, improvements were seen in ALT, AST, GGT, glucose, triglycerides, HOMA-IR and BMI, but not in liver fibrosis score.[23] From a meta-analysis of 33 studies (RCTs and observational studies), endoscopic-bariatric and metabolic therapies reduced body weight (MD -12·18 kg, 95% CI -15·42 to -8·93, 22 studies, 1224 participants).[24]	interventions (15 behavioural weight loss programmes, 6 pharmacotherapy, and 1 surgery) with 2588 participants with NAFLD, weight loss interventions were associated with improvements in biomarkers including ALT, histologically or radiologically measured liver steatosis, histological NAFLD activity score, and presence of NASH.[26] In the TREATY-FLD RCT of 88 patients with obesity and NAFLD, time-restricted eating did not produce additional benefits for reducing intrahepatic triglyceride content, liver stiffness, body weight, and metabolic risk factors compared with daily calorie restriction.[27] In a meta-analysis of 3 RCTs involving 458 patients with NAFLD, semaglutide reduced body weight (mean difference -6·53 kg, 95% CI -11·21 to -1·85) compared with placebo, and had beneficial histological, radiological, liver enzyme, and cardiometabolic effects.[28]

					In the E-LIFT RCT of 50 patients with T2D and NAFLD, compared with the control group, empagliflozin reduced liver fat (MRI-PDFF) and improved ALT, although there was no significant between-group difference in weight change from baseline to 20 weeks (p=0·154).[29] From a phase IIa RCT, comparing the GLP-1–glucagon receptor co-agonist efinopegdutide with semaglutide in 145 patients with NAFLD, the least squares mean relative reduction from baseline in liver fat content at week 24 was significantly greater (p<0·001) with efinopegdutide (72·7%) than with semaglutide (42·3%). Both treatment groups had an LS mean percent reduction from baseline in body weight at week 24 (efinopegdutide 8·5% vs semaglutide 7·1%; p=0·085).[30]

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Table S5. A summary of key pieces of evidence from epidemiology, genetics, and interventions (observational and limited RCTs) to support further testing of weight loss modalities in key mental health conditions

	EPIDEMIOLOGY		GENETICS	INTERVENTIONS	
	Incident disease	**Prevalent disease**		**Observational data on weight loss**	**Randomised trials of weight loss**
Depression	From fourteen longitudinal studies including over 140 000 adults, those living with obesity had an 18% increased risk of being depressed (RR 1·18, 95% CI 1·04-1·35).[1] From 15 longitudinal studies (n=58 745), obesity at baseline increased the risk of onset of depression (unadjusted OR 1·55, 95% CI 1·22-1·98; p<0·001). Overweight increased the risk of onset of depression (unadjusted OR 1·27, 95% CI 1·07-1·51; p<0·01).[2] In 34 653 US adults, women living with overweight and with obesity were at increased risk of incident major depressive disorder during follow-up (3-year) with OR 1·3, 95% CI 1·02-1·56 and 1·2, 95% CI 1·02-1·51, respectively.[3] From six longitudinal studies including 20 855	From summary of 6 meta-analyses combining up to 26 cross-sectional studies, the pooled OR of depression among individuals living with obesity ranged from 1·23 to 1·41 in studies based on self-reported symptoms, and from 1·14 to 1·30 in studies based on clinical diagnoses.[7] From a meta-analysis of 18 cross-sectional studies including 371 897 individuals, obesity (defined by BMI ⩾30 kg/m²) was associated with depression (defined by symptoms) with pooled OR 1·29 (95% CI 1·18-1·42).[8] From 177 047 participants (aged ⩾18 y) in the BRFSS (Behavioral Risk Factor Surveillance System), the prevalence of 3 psychiatric disorders (current depression,	In meta-analysis of 8 Mendelian randomisation studies, there was an increased risk of depression associated with obesity (OR 1·33; 95% CI 1·19-1·48).[11] From a genome-wide association study of 694 649 people of European ancestry from the GIANT consortium, main Mendelian randomisation results suggested higher BMI or WHR was positively causally associated with an increased risk of major depressive disorder.[12] Based on a Mendelian randomisation study using 48 791 individuals with depression and 291 995 controls in the UK Biobank, higher BMI was strongly associated with higher odds of depression, especially in women.[13] Using a 73-variant BMI genetic risk score, a genetically determined one standard deviation higher BMI (4·9 kg/m^2) was	From 24 longitudinal studies, majority of these studies showed that weight loss, whether through calorie restriction, dietary supplements, or behavioural training, resulted in a reduction of depressive symptoms.[15]	From a pre-post low-calorie diet (LCD) intervention meta-analysis of 25 studies (of which 21 were RCTs) including 4574 participants at baseline and 4134 at follow-up, depression scores were significantly lower following a LCD (SMD = -0·47; 95% CI -0·59 to -0·35; p<0·001), which was not significantly moderated by the addition of exercise or behavioural therapy as a non-diet adjunct.[16] From a meta-analysis of four RCTs with 183 participants, there was no significant change in depression between exercise and control groups.[17] In a meta-analysis of 31 RCTs (N=22 in T2DM and N=9 in obesity), mean duration 91 weeks, 84 713 patients, no significant difference was observed

	adolescents, those living with obesity had a 40% increased risk of being depressed (RR 1·40, 95% CI 1·16-1·70).[4] Among 3090 elderly French participants who were depression-free at baseline and followed for 10 years, subjects with high BMI at follow-up had an increased risk of developing depression with RR 1·60, 95% CI 1·03-2·51.[5] In longitudinal PREVEND study of 1094 participants with 2-year follow-up, obesity (BMI ⩾30 kg/m²) was associated with recurrent major depressive disorder (OR 11·63, 95% CI 1·05-128·60) but not for single episode of MDD.[6]	lifetime diagnosed depression and anxiety) was significantly higher in women living with overweight (BMI 25 to <30) or obesity (BMI ⩾ 30), and in men who had class III obesity (BMI ⩾ 40 kg/m²) than in those of a healthy BMI (18·5 to <25 kg/m²).[9] From a meta-analysis of 8 cross-sectional studies including 176 510 individuals, obesity (defined by BMI ⩾30 kg/m²) was associated with depression (clinically diagnosed) with pooled OR 1·16 (95% CI 1·02-1·32).[8] In a cross-sectional study of 140 564 UK Biobank participants, the fully adjusted odds ratio for participants with obesity associated with probable major depression was 1·16, 95% CI 1·12-1·20 using BMI, 1·15, 95% CI 1·11-1·19 using WC, 1·09, 95% CI 1·05-1·13 using WHR and 1·18, 95% CI 1·12-1·25 using body fat percentage.[10]	associated with higher odds of depression in all individuals OR 1·18, 95% CI 1·09-1·28, p=0·00007 and women only OR 1·24, 95% CI 1·11-1·39, p=0·0001. In two-sample Mendelian randomisation in up to 145 668 European participants from the UK Biobank, a genetically determined one standard deviation higher BMI (4·6 kg/m^2) was associated with higher odds of current depression OR 1·50, 95% CI 1·15-1·95).[14]		between GLP-1RA and placebo [MH-OR 0·97, 95% CI 0·83-1·15, p=0·76] on psychiatric adverse events, and with no difference between trials enrolling only patients with diabetes, or overweight or obesity.[18] GLP-1RA treatment was not associated with a significant difference in the risk for overall suicidal episodes [MH-OR 0·86, 95% CI 0·47-1·56, p=0·61]. In 17 trials enrolling 58618 patients, there was no significant association between GLP-1RA therapy and depression [MH-OR 0·96, 95% CI 0·68-1·35, p=0·82].

		From six cohort studies, people with BMI 25-29·9 kg/m^2 had pooled OR 1·02 (95% CI 0·84-1·23) with discrepant results in subgroups by men OR 0·84 (95% CI 0·72-0·97) and women OR 1·16 (95% CI 1·07-1·25). WC >102 cm (men) or >88 cm (women) pooled OR for subsequent depression was 1·38 (95% CI 1·17-1·62).[8]			
Fibromyalgia	Obesity is associated with increased incidence of fibromyalgia. In a longitudinal study of 15 990 women without fibromyalgia at baseline followed for 11 years in the Norwegian Nord-Trøndelag Health Study, women living with overweight or obesity had a 60-70% higher risk of developing fibromyalgia compared with women with healthy weight.[19] Obesity may worsen several key domains of fibromyalgia including pain, fatigue, sleep disturbance, and quality of life.[20]	Obesity is prevalent in fibromyalgia with results from a large systematic literature review and meta-analysis estimating the overall prevalence of obesity in fibromyalgia is 35·7%, rising to 43% in the USA.[20]	A Mendelian randomisation of data from the FinnGen consortium revealed that genetic variants associated with body fat percentage (OR=1·524, 95% CI: 1·153–2·013) and BMI (OR=1·542, 95% CI: 1·271–1·872) were associated with an increased risk of fibromyalgia, suggesting a causal association between obesity and fibromyalgia.[21]	Preliminary evidence suggests intentional weight loss may improve symptoms in fibromyalgia, although more definitive evidence is needed via larger, randomised controlled studies. A pilot study of women with fibromyalgia and BMI $\geqslant$25 kg/m^2 investigated the effects of behavioural weight loss treatment on fibromyalgia symptoms. The results showed that individuals lost an average of 9·2 lb (4·4%) body weight over 20 weeks and noted improvement in several fibromyalgia domains including less depression, pain, pain interference, anxiety, and improved quality of life.	Randomised controlled trials of weight loss to treat fibromyalgia are limited. In a single-blind randomised controlled trial, 83 participants with fibromyalgia living with obesity were randomised to a dietary weight reduction group (n=41), advised to follow a conventional energy-restricted diet of about 1200 kcal/day for 6 months, or to a control group (n=42) given healthy eating advice without calorie restriction. The results showed weight loss led to significant improvement in quality of life with improvement in fibromyalgia impact questionnaire (FIQ). Depression, sleep quality,

				While encouraging, this study was of small sample size (52 women enrolled, 42 started the study and 31 completed the treatment programme), and there was no control group for comparison.[22] In a separate observational study of 123 participants living with obesity referred to a behavioural weight management programme, which included an initial 12-week very-low-calorie (800 kcal/day) liquid meal replacement, participants lost an average 16% of their baseline body weight. Pain (p=0·022), symptom severity (p=0·004), depression (p<0·001), and fibromyalgia scores (p=0·004) improved following weight loss. Those who lost at least 10% of their body weight showed greater improvement in fibromyalgia symptoms.[23] While encouraging and including a larger sample size, again this study was limited by a lack of a comparator control group. A propensity-matched retrospective study of the	and tender point count also improved significantly with weight loss.[26]

				TriNetX research network (48 025 people with fibromyalgia in each cohort, followed for 5 years) found that GLP-1 receptor agonist use was associated with reduced odds of opioid prescription (OR 0·65), of pain diagnostic codes (OR 0·79), and of fatigue diagnostic codes (OR 0·68; all $p<0·001$), with no significant difference in disability-related codes.[24] However, despite propensity matching, these observational findings may still be subject to residual confounding and require confirmation through an appropriately powered RCT. Bariatric surgery has been associated with improvements in fibromyalgia, as reported in a small retrospective chart review of patients with fibromyalgia who underwent laparoscopic Roux-en-Y gastric bypass.[25] The postoperative decrease in median BMI from 49·4 to 29·7 kg/m² was significant ($p=0·0010$) and was associated	

				with significant improvements in median pain score (p=0·0010) and median points of tenderness (p=0·0010).	

Table S5 References

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