# Narrative synthesis

A total of 2,144 studies were not included in the meta-analyses. Using the 16 categories used to group outcomes, these effects are summarised here, in alphabetical order with the "other" category at the end. Where there are many studies, a summary of the directions of effect are given. Given that studies use a variety of transformations, units, and models, comparison of the magnitude of effect is not appropriate. Instead, the focus here is on directions of effect estimates and whether evidence is consistent across studies. Evidence for selected exposure-outcome pairs is also summarised. For a complete picture, or to look at specific exposure-outcome pairs, data are available on [GitHub](https://github.com/mattlee821/systematic_review_MR_adiposity/blob/main/analysis/002_data.csv) and can be [browsed online](https://mattlee.shinyapps.io/SR_meta_analysis_browser/).

### Anthropometric

A total of 85 studies were reported across nine articles for anthropometric outcomes. These studies were generally investigating the effect of maternal adiposity on offspring anthropometric traits. This included analyses of birthweight, BMI, hip circumference adjusted for BMI (HCadjBMI), waist circumference adjusted for BMI (WCadjBMI), and WHRadjBMI on similar anthropometric traits such as adipose tissue volume, birth length, body fat, head circumference, leg fat, and trunk fat. Most effect estimates were positive (N = 60; negative = 24). A single MR analysis (BMI on offspring BMI) had an effect estimate of 0. A number of other analyses focussed on offspring traits as the outcome with both positive and negative effect estimates. The study by Winkler et al. (2018)1 used a unique instrumentation method, using a composite measure of BMI, WHR, and WHRadjBMI, for example BMI increasing and WHR increasing SNPs were used as a genetic instrument. Generally, the effect of adiposity on anthropmetric traits was to increase them, but this is likely a reciprocal relationship, i.e., increased BMI leads to increased WHR and increased WHR leads to increased BMI.

### Cancer

A total of 332 studies were reported across 39 articles for cancer-related outcomes. This included analyses of all cancers, cancer mortality, cancer types such as breast and prostate, and subtypes such as ER- and ER+ breast cancer. Most effect estimates were positive (N = 189; negative = 137), while six studies of breast, kidney, lung, and prostate cancer showed effect (odds ratio) estimates approximately equal to 1. Most analyses with positive effect estimates had CIs which spanned the null. The same was true for negative effect estimates.

Of the 31 cancer outcomes, three showed negative effect estimates -- cervical (with BMI and WHRadjBMI), clear cell (with BMI), and gastric (with BMI) cancers -- while 14 showed positive effect estimates. This included overall cancer mortality (with BMI) and cancer risk (with BMI). The remaining cancer types with positive effect estimates included Barrett's esophagus (with BMI), colon (with BMI), esophageal (with BMI), lymphoid (with BMI), meningioma (with BMI, WC, and BF), rectal (with BMI), renal (with BMI, WHR, and BF), skin (including melanoma; with BMI), and stomach and esophageal (with BMI). Low malignant potential tumors also showed a positive effect estimate with BMI. The remaining 13 cancer types had positive and negative effect estimates. This included any cancer, breast, colorectal, endometrial, glioma, kidney, lung, multiple myeloma, ovarian, pancreatic, prostate, testicular, and upper aerodigsetive cancers.

Results suggest adiposity increases overall cancer risk and risk of mortality. However, this risk is modulated by cancer type and subtype. In the case of cancers with only negative effect estimates, these cancers were only analysed once, whereas cancers like breast and lung, which were measured multiple times, showed both positive and negative effect estimates.

### Cardiovascular

A total of 274 studies were reported across 50 articles for cardiovascular-related outcomes. This included analyses of 11 continuous and 19 binary outcomes. Exposures included birth weight, BMI, body fat mass measures, HC, WC, WCadjBMI, weight, WHR, and WHRadjBMI.

In total, 83 studies investigating the effect of adiposity with continuous traits were reported across 22 articles. Most of these studies reported positive effect estimates (N = 69; negative = 14). Of the 11 traits, four had a single reported MR result (left ventricular mass, mean arterial pressure, pulse pressure, and pulse wave velocity) -- all had positive effect estimates except pulse wave velocity. Of the seven remaining traits, five had both positive and negative effect estimates. Effects on heart rate were negative with wide CIs, while effects on carotid-intima media thickness (IMT) were positive with some studies reporting effect estimates with CIs that did not overlap the null for BMI and WHRadjBMI.

Of the five traits with positive and negative effect estimates, diastolic blood pressure (DBP) showed a negative effect estimate solely in relation to the effect of birthweight, and SBP showed weak evidence for a decreasing effect of BMI and birthweight. There was much stronger evidence for an increasing effect on SBP and DBP across BMI, WHR, and WHRadjBMI. The positive and negative effect estimates associated with heartbeat were associated with CIs which spanned the null for both BMI and WHRadjBMI. For carotid IMT, evidence appeared stronger, with narrower CIs which did not span the null, for an increasing effect of BMI. Evidence for an effect of BMI and WHRadjBMi on left ventricular hypertrophy was weak and dependent upon the method used to assess hypertrophy.

In total, 191 studies investigating the effect of adiposity with binary outcomes were reported across 35 articles. Nine of these studies were from a single article which only reported p-values for the association between BMI and CAD. Of the remaining 182 studies, the majority reported positive effect estimates (N = 139; negative = 43). There was strong evidence across multiple studies for the effect of BMI on CAD and CVD, and results also supported an effect of WHRadjBMI, WCadjBMI, and WHR. Though there was evidence for an effect of BMI on heart failure, there was weak evidence for a similar effect of WHRadjBMI on the same outcome. There was strong evidence for an effect of fat mass and fat free mass on increased risk of arrythmia, but only weak evidence for a similar effect from WHRadjBMI and birthweight. There was conflicting evidence for an effect of increased BMI on myocardial infarction (MI). When using BMI increasing and WHR decreasing instruments MI risk decreased while when using BMI and WHR increasing instruments, MI risk increased. There was also weak evidence of increased birthweight reducing MI risk. There was strong evidence across many different adiposity measures for an increased risk of deep vein thrombosis (DVT).

Though there were some conflicting results, BMI and MI for example, and some analyses reported both positive and negative effect estimates for the same exposure-outcome pairs, BMI and SBP for example, on balance reported results support an increasing effect of adiposity on cardiovascular traits. Evidence was strongest for the effect of adiposity on CAD, CVD, and DVT.

### Gastrointestinal

A total of 17 studies were reported across 5 articles for gastrointestinal-related outcomes. This included analyses of inflammatory bowel disorders, *Helicobacter pylori* infection measures, gallstone disease, and peptic ulcers. All but one analysis of the effect of BMI on irritable bowel syndrome had a positive direction of effect. There was evidence for an effect of birth weight on inflammatory bowel disease and some evidence for an effect of BMI on peptic ulcers, however weak evidence for an effect of WHRadjBMI on peptic ulcers. All other analyses showed weak evidence of effect. As no exposure-outcome pairs were analysed by more than one study, it is hard to draw conclusions from the available evidence, however effect estimates were mostly positive across studies.

### Hepatic

A total of 71 studies were reported across six articles for hepatic-related outcomes. In total, 11 outcomes were reported, of which the majority of analyses (N = 40) were for three liver markers: alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl Transferase (GGT). All but two binary outcomes (the effect of low BMI and low alcohol consumption on liver disease) had positive directions of effect. 14 of the 40 MR analyses investigating liver markers had negative directions of effect. AST was reported once with strong evidence of a reducing effect of BMI. Analyses of ALT and GGT used multiple measures across multiple studies, for example adjusting for alcohol consumption. Results support an increasing effect of increased BMI on ALT and GGT, which persisted after adjustment for alcohol consumption. The remaining eight outcomes were only investigated by a single article. Evidence was found for BMI and WHR on chronic liver disease and BMI, WHR, and WHRadjBMI on non-alcoholic fatty liver disease (NAFLD). There was strong evidence for an increasing effect of adiposity on all hepatic traits.

### Inflammation and immunity

A total of 12 studies were reported across five articles for immune-related outcomes. In total, eight outcomes were reported. Seven studies reported negative directions of effect; five studies reported positive directions of effect. There was weak evidence for an effect of adiposity on all outcomes, except for an increasing effect of BMI on dermatophytosis (though weak evidence for an effect of WHRadjBMI) and BMI on psoriasis.

### Mental health

A total of 124 studies were reported across 22 articles for mental health-related outcomes. A total of 66 studies reported positive directions of effect; 38 studies reported negative directions of effect; 4 studies reported effect estimates equal to 0; the remaining studies did not report an effect estimate. In total, 27 outcomes were reported, though 16 of these were reported only once - all showed weak evidence of an effect (e.g., attention deficit hyperactivity disorder, anorexia nervosa, being a worrier/nervous person, body dissatisfaction (evidence from weight and shape concern analyses showed a negative effect of BMI), and happiness). Of the remaining 11 outcomes, the majority of analyses focussed on depression. Across the 11 articles that looked at depression, there was strong evidence for an effect of adiposity increasing depression. When excluding non-neuronal SNPs (which will influence adiposity at a cellular as opposed to behavioural level), the effect of BMI was reduced and CIs crossed the null2. This would suggest that the association with depression is not a result of behavioural changes associated with adiposity. Rather, the association is likely due to the physicality of adiposity and probably the stigmatization associated with that. There was weak evidence for an effect of BMI on anxiety. There was weak evidence for an effect of increased BMI on increased loneliness. Similarly, there was weak evidence for a decreasing effect of BMI, WHR, WC, and BF on subjective well-being. There was some evidence for a decreasing effect of BMI and WHR on stress/nervous feelings, however weak evidence was found for all other psychological distress traits. Binge eating and overeating increased because of increased BMI. On balance, there appears to be an association between adiposity and mental health traits, particularly body image-related traits.

### Metabolic

A total of 380 studies were reported across 51 articles for metabolic-related outcomes. A total of 111 outcomes were investigated across the 380 studies, the majority of which were metabolites. Most metabolites investigated were nuclear magnetic resonance derived lipids and although most metabolite effect estimates were positive, CIs for many spanned the null. There was, for example, weak evidence for an increasing effect of BMI on cholesterol, however strong evidence for an effect of WHRadjBMI. C-reactive protein (CRP) was investigated with BMI across 9 studies with all but two reporting strong evidence for an increasing effect of BMI on CRP levels. BMI was found to decrease levels of apolipoprotein A-I and increase apolipoprotein B levels; there was weak evidence for an increasing effect of BMI and WHRadjBMI on apolipoprotein A-IV. There was strong evidence for a decreasing effect of BMI, WHRadjBMI, and birth weight on HDL levels; there was weaker evidence for an overall effect of adiposity on LDL -- WHRadjBMI was strongly associated with an increase in LDL, while birth weight showed a decreasing effect on LDL. BMI showed weak evidence of both increasing and decreasing effects on LDL. There was also strong evidence for an increasing effect of BMI, WHR, and WHRadjBMI on triglycerides (TG).

There was strong evidence for an effect of increased BMI, WHR, WHRadjBMI on fasting glucose; there was weaker evidence for an effect of childhood BMI and birth weight on fasting glucose. There was weak evidence for an effect of BMI (adult and childhood) on two-hour glucose test (there was evidence for a decreasing effect of birth weight), and weak evidence for an increasing effect of BMI on non-fasting glucose. There was strong evidence for an effect of BMI on hyperuricaemia as well as uric acid. Weaker evidence was reported for an effect of BMI (adult and childhood) and WHRadjBMI on glomerular filtration rate, creatine, and creatinine. There was strong evidence for an increasing effect of BMI, WHR, and WHRadjBMI on fasting insulin. There was however weak evidence for an increasing effect of BMI on insulin secretion. Binary outcomes reported broadly increasing effects of adiposity. For example, there was strong evidence for an effect of increased BMI on increased diabetes (type-1, type-2, and all). Similarly strong evidence was reported when using birth weight, childhood BMI, WHR, WHRadjBMI, and WC. Strong evidence for an effect of BMI and WHRadjBMI on increased dyslipidemia and metabolic syndrome was reported, but there was weak evidence for an effect of BMI and WHRadjBMI on hyper- and hypo-thyroidism and iron deficiency. The effect of adiposity appears far reaching in regard to metabolic traits. This effect is generally to increase levels of traits that are themselves associated with poor health outcomes.

### Neurological/behavioural

A total of 67 studies were reported across 21 articles for brain-related outcomes. This included analyses of Alzheimer's disease, amyotrophic lateral sclerosis (ALS), dementia, multiple sclerosis (MS), Parkinson's disease, and stroke. Bipolar disorder, schizophrenia, cognitive ability, grey matter volume, and migraine were also present. Exposures included birth weight, BMI, WHR, and WHRadjBMI - BMI was used in most analyses. Most effect estimates were positive (N = 45; negative = 17). Two analyses (BMI on stroke (ischemic small vessel) and dementia) had an OR of 1. Effect estimates appeared larger overall when in the positive direction, however in many cases across both the positive and negative estimates, CIs spanned the null. On balance, results suggest adiposity increases the risk of all types of stroke. However, for all other outcomes, there appears conflicting or weak evidence for an effect.

### Renal

A total of 34 studies were reported across four articles for renal-related outcomes. Only one study, the effect of WHRadjBMI on renal failure, reported a negative direction of effect. All other studies reported a positive direction of effect. Most analyses looked at renal failure (N = 20) which showed strong evidence for an increasing effect of BMI, WHR, and WHRadjBMI. These analyses were however from a single article3. A similar picture is present for BMI and renal disease which was investigated by a single article4, as well as macroalbuminuria and BMI4. There was weak evidence for an increasing effect of childhood BMI and birth weight on chronic kidney disease. As few articles looked at renal-related outcomes, it is difficult to draw conclusions given a lack of replication. However, the general trend is for an increasing effect of adiposity on the risk of renal-related traits and renal diseases.

### Reproductive

A total of 17 studies were reported across five articles primarily for menarche (age at and early onset). All studies reported positive directions of effect except for the two studies on age at menarche. The two studies reporting on age at menarche and BMI and childhood BMI found strong evidence that adiposity decreased age at menarche5,6, which is associated with poor health outcomes in later life. The remaining 15 analyses on early menarche were reported by one study7 and showed evidence that BMI, total body fat, fat free mass, sum of skinfolds, HC, and WHR all lead to an earlier menarche. One study reported evidence of an increasing effect of BMI on polycystic ovary syndrome (PCOS)8, while another reported weak evidence for an increasing effect of WHRadjBMI on uterine fibroids9. There is clear evidence that adiposity increases the likelihood of early menarche.

### Respiratory

A total of 316 studies were reported across 13 articles for respiratory-related outcomes. Most of these analyses were for smoking outcomes (N = 175) such as age at initiation, status, number of cigarettes per day, as well as comparisons between smoking statuses (e.g., ever vs never). Of the non-smoking respiratory studies, 11 studies reported negative directions of effect, the remaining 123 reported positive directions of effect. Of the smoking respiratory studies, 81 reported negative directions of effect and 90 reported positive directions of effect. There was strong evidence for an effect of BMI, WHR, and WHRadjBMI on current smoking status. There was also evidence for a positive effect of BMI on lifetime smoking. There was weak evidence for an effect of BMI on former vs current and experimental vs never smoking. There was some evidence for an effect of BMI on ever vs never smoking, increasing the odds of being an ever smoker. There was similarly an increasing effect on ever being a smoker for BMI, WC, and BF -- this effect modulated when including/excluding neuronal/deprivation related SNPs. Most of the remaining studies were for asthma and asthma subtypes. There was broadly weak evidence for an increasing effect of BMI on asthma. There was some evidence for an increasing effect of BMI on chronic obstructive pulmonary disorder as well as for an increasing effect of BMI on wheezing, and decreased lung volume measures (forced vital capacity and forced expiratory volume). Overall adiposity appears to increase the likelihood of being a smoker as well as having respiratory conditions such as asthma.

### Skeletal

A total of 93 studies were reported across 13 articles for skeletal-related outcomes. A total of 20 studies reported negative directions of effect; 70 reported positive directions of effect; three did not report an effect estimate. Most studies were for arthritic outcomes (arthritis and osteoarthritis), though evidence was conflicting. There was some evidence for an increasing effect of BMI on rheumatoid arthritis and gout, however weak evidence for an effect of WHRadjBMI. Strong evidence was reported for an increasing effect of BMI, WC, and HC on osteoarthritis (self-report, hospital diagnosed: hip, knee), however weak evidence for an effect of WHR and birth weight. One study reported an effect of BMI on osteoporosis, where there was evidence of an increasing effect. There was strong evidence for an increasing effect of BMI and fat mass on bone mineral density (including site-specific bone mineral density), and some evidence for an increasing effect of trunk fat mass on bone mineral content. On balance, the effect of adiposity was to increase skeletal traits. This is especially true for arthritic traits, where body composition as opposed to deposition appears to be more important.

### Skin

A total of 16 studies were reported in one article10. Budu-Aggrey et al., (2019) investigated the effect of BMI on psoriasis using one- and two-sample MR analyses. To strengthen evidence for a causal effect, they meta-analysed one- and two-sample MR results and performed the reverse MR investigating the effect of psoriasis on BMI. All studies reported a positive direction of effect. There is some evidence for an increasing effect of BMI on psoriasis and weak evidence for an effect of psoriasis on BMI. However, these results come from a single study and caution around interpretation is needed.

### Social

A total of 71 studies were reported across 12 articles for social-related traits such as income, education, and employment. A total of 14 studies investigated the effect of adiposity on income, nine of these reported a negative direction of effect and five reported a positive direction of effect. Of the remaining 57 non-income related studies, 41 reported a negative direction of effect, 12 reported a positive direction of effect, and four reported an effect estimate of 0. Overall, there was evidence across 12 studies for a decrease in income as a result of increased BMI. There was weak evidence for an effect of BMI on cohabitation and for an increasing effect on socioeconomic status. Evidence was conflicting for an effect of BMI on education traits such as years in education and degree status. There was weak evidence for a decreasing effect of BMI on employment traits such as years employed, employment status, and job class. There was weak evidence for a decreasing effect of BMI on risk taking behaviour, and satisfaction with family, friends, finances and work. However, there was evidence for a decreasing effect on health satisfaction. On balance, the effect of adiposity seems detrimental for social-related traits.

### Other

Where outcomes could not easily be grouped into one of the previous categories, there were grouped into the "other" category. A total of 235 studies were reported across 82 articles for outcomes that could not easily be grouped into one of the previous categories. A total of 65 studies reported a negative direction of effect, 86 reported a positive direction of effect, the remaining studies were for methylation sites and did not report an effect estimate. A majority (N = 118) of studies were a hypothesis-free investigation of the effect of BMI on DNA methylation. Few of these analyses reported an effect estimate (N = 34). Of those reporting an effect estimate, a positive direction was reported for 13 studies and a negative direction for 21 studies. There was weak evidence for an effect of BMI. Of the remaining 117 studies, 68 looked at the effect of BMI on mortality and cause specific mortality. There was weak evidence for an effect of BMI on cause specific mortality across the board, including for all cancer, all cardiovascular, cancer specific, respiratory, and stroke. There was also weak evidence for an effect on all-cause mortality.

Of the remaining 49 studies, there was weak evidence for an effect of increased BMI on multiple sleep traits (over-/under-sleeper, hours slept, chronotype etc.). There was however evidence for an increasing effect of BMI on daytime sleepiness. There was some evidence for a decreasing effect of BMI on physical activity, including moderate to vigorous physical activity. Fat mass index showed similar effects; however childhood BMI did not appear to show a similar effect on physical activity. There was weak evidence for an effect of BMI on cataract and macular degeneration.

# References

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