



Lee, M., Hatcher, C. A., McGuinness, L., McBride, N. S., Battram, T. M., Wan, W., Fang, S., Wade, K. H., Corbin, L. J., & Timpson, N. J. (in press). Systematic review and meta-analyses: What has the application of Mendelian randomization told us about the causal effect of adiposity on health outcomes? *Wellcome Open Research*, 7(308). <https://doi.org/10.12688/wellcomeopenres.18657.1>

Early version, also known as pre-print

Link to published version (if available):  
[10.12688/wellcomeopenres.18657.1](https://doi.org/10.12688/wellcomeopenres.18657.1)

[Link to publication record on the Bristol Research Portal](#)  
PDF-document

This is the submitted manuscript (SM). It first appeared online via Wellcome Open Research at <https://doi.org/10.12688/wellcomeopenres.18657.1>. Please refer to any applicable terms of use of the publisher.

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1 Systematic review and meta-analyses: What has the application of Mendelian randomization told us  
2 about the causal effect of adiposity on health outcomes?

3

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12

13 **Abstract**

14 Mendelian randomization (MR) is increasingly used for generating estimates of the causal  
15 impact of exposures on outcomes. Evidence suggests a causal role of excess adipose tissue  
16 (adiposity) on many health outcomes. However, this body of work has not been  
17 systematically appraised.

18

19 We systematically reviewed and meta-analysed results from MR studies investigating the  
20 association between adiposity and health outcomes prior to the SARS-CoV-2/COVID-19  
21 pandemic (PROSPERO: [CRD42018096684](https://doi.org/10.1111/CRD4.2018096684)). We searched Medline, EMBASE, and bioRxiv  
22 up to February 2019 and obtained data on 2,214 MR analyses from 173 included articles.  
23 29 meta-analyses were conducted using data from 34 articles (including 66 MR analyses)  
24 and results not able to be meta-analysed were narratively synthesised.

25

26 Body mass index (BMI) was the predominant exposure used and was primarily associated  
27 with an increase in investigated outcomes; the largest effect in the meta-analyses was  
28 observed for the association between sex-combined BMI and female-specific polycystic  
29 ovary syndrome (estimates reflect odds ratios (OR) per standard deviation change in each  
30 adiposity measure): OR = 2.55; 95% confidence interval (CI) = 1.22–5.33. Only colorectal  
31 cancer (sex-combined) was investigated with two exposures in the meta-analysis: BMI (sex-  
32 combined; OR = 1.18; 95% CI = 1.01–1.37) and waist-hip ratio (sex-combined; WHR; OR  
33 = 1.48; 95% CI = 1.08–2.03). Broadly, results were consistent across the meta-analyses and  
34 narrative synthesis.

35

36 *Consistent with many observational studies, this work highlights the impact of adiposity*

37 *across a broad spectrum of health outcomes, enabling targeted follow-up analyses.*

38 *However, missing and incomplete data mean results should be interpreted with caution.*

39

40 Keywords

41 Systematic review, epidemiology, Mendelian randomization, adiposity, obesity

## 42 Introduction

43 Observational epidemiological studies have indicated that adiposity is strongly associated  
44 with all-cause and cause-specific mortality<sup>1,2</sup> as well as numerous health outcomes<sup>3</sup>. This  
45 includes many common diseases, such as cardiovascular disease (CVD)<sup>4</sup> and many cancers<sup>5</sup>,  
46 as well as commonly accepted risk factors for diseases such as high blood pressure<sup>6</sup>.  
47 Mendelian randomization (MR) studies can be used alongside conventional observational  
48 studies to strengthen evidence for causality within an association (or indeed provide  
49 evidence against an association)<sup>7</sup>, and there has been a steady increase in their publication  
50 since being widely reported on in 2003<sup>8</sup>. There is now a large body of evidence from MR  
51 studies for a causal effect of adiposity on many outcomes, including many cancers<sup>9,10</sup>.

52

53 Systematic reviews enable a global overview of the literature and provide avenues for  
54 hypothesis generation. In combination with meta-analyses, systematic reviews can be used  
55 as a method for improved causal inference as pooled estimates can be more precise than  
56 estimates from individual studies<sup>11</sup>. As the MR literature has not been systematically  
57 appraised with respect to the association between adiposity and health outcomes, we set  
58 out to systematically review MR studies investigating adiposity as an exposure and provide  
59 pooled estimates where appropriate. During the recent severe acute respiratory  
60 syndrome coronavirus 2/coronavirus disease 2019 (SARS-CoV-2/COVID-19)  
61 pandemic, there was an explosion of work focused on body mass index (BMI) related  
62 traits and outcomes/intermediates or infection impact. This is extremely important,  
63 but is complicated by both the parameterisation of infection as a target and the

64 nature of exhaustive genetic instruments for adiposity. This work has been brought  
65 together to recount the body of work undertaken immediately before this event and  
66 hence presents a pre-pandemic overview of the literature. Further work is now, of  
67 course, needed to distil the post-pandemic literature; however, that is not within  
68 the remit of this review.

69

70 Here, a hypothesis-free systematic review and meta-analyses are presented alongside a  
71 narrative synthesis of 173 articles reporting 2,214 MR analyses. This work was pre-  
72 published on [PROSPERO](#) (Extended Data File 1), is accompanied by Extended Data  
73 ([10.5281/zenodo.7377442](#)), and a [GitHub repository \(10.5281/zenodo.7377406\)](#) and [data](#)  
74 [browser](#) where all data, scripts, results, and figures are available. A narrative synthesis of  
75 non-meta-analysed studies is given in Extended Data 6.

## 76 **Methods**

### 77 *Data sources and search strategy*

78 EMBASE and MEDLINE were searched from inception (EMBASE = 1974; MEDLINE =  
79 1946) until 18 February, 2019 using detailed search strategies including free text and  
80 controlled vocabulary terms, and used synonyms for both adiposity and MR terms  
81 (Extended Data File 2 and on [GitHub](#)). The pre-print service, bioRxiv, was also searched  
82 from inception (November 2013) until 18 February, 2019. Due to the limited search  
83 functionality and inability to include Boolean operators ('AND', 'OR', 'NOT') in bioRxiv  
84 searches, four free-text terms in four independent searches were used: 'Mendelian  
85 randomization', 'Mendelian randomisation', 'causal inference', and 'causal analysis'.

86

### 87 *Study selection*

88 Articles returned through the searches of EMBASE and MEDLINE were imported into  
89 EndNote (version X8.2; Clarivate Analytics), and de-duplication was performed using  
90 pagination identifiers<sup>12</sup>. Articles returned from bioRxiv were imported into Mendeley and  
91 de-duplication performed using the Mendeley de-duplication function. Titles and abstracts  
92 of all remaining articles were screened by two independent reviewers (MAL and LJM)  
93 using Rayyan<sup>13</sup>, with discrepancies resolved through discussion. Articles that met the pre-  
94 defined inclusion criteria (see below) were combined and, in instances where the bioRxiv  
95 study had been published and this was identified in either the EMBASE or MEDLINE  
96 search, the bioRxiv version of the study was excluded. The full texts of all studies that met  
97 inclusion criteria were then screened by the two reviewers.

99 For title and abstract screening and for full-text screening, articles must have met the  
100 following pre-defined inclusion criteria: be written in English; be available in full text (or  
101 in the case of conference abstracts, the authors must be contactable to obtain the relevant  
102 data); be published in a peer-reviewed journal or bioRxiv; use MR methodology to  
103 investigate the causal effect of adiposity on any outcome. Adiposity was considered to be  
104 any measure which aimed to assess the amount of adipose tissue an individual possessed. If  
105 a study focused on adiposity alongside other exposures, the effect of each adiposity measure  
106 was reported separately if available. If it was not available, the joint effect was reported.  
107 Articles in which an MR approach was used but not explicitly called ‘Mendelian  
108 randomization’ were included. More specifically, any study in which genetic variants were  
109 used as instrumental variables (IVs) or the direct association between a genetic variant and  
110 outcome was employed was eligible (as described previously<sup>8</sup>), provided it met the other  
111 inclusion criteria.

112

### 113 *Data extraction*

114 In the first instance, data extraction was performed by eight reviewers (MAL, CH, LJM,  
115 NM, TB, WW, SF, and KHW), with articles split evenly between them, using a data  
116 extraction form (Extended data 3) designed using a pre-publication version of the STROBE-  
117 MR guidelines<sup>14</sup> in order to obtain all relevant data from each study. Once all articles had  
118 been reviewed, two reviewers (MAL and CH) extracted data from all articles they did not  
119 review in the first instance. The same two reviewers then checked all extracted data for



120 discrepancies, which were resolved through a third review of individual articles and  
121 subsequent discussion. In some cases, articles included in the data extraction contained  
122 more than one relevant MR analysis. As such, the words “study” and “studies” refer to the  
123 MR analyses within an article. The following data were extracted from each of the studies  
124 from all contributing articles: exposure(s), outcome(s), study design and sample  
125 characteristics, genetic variant IV selection, MR methodology, sensitivity analysis, and  
126 causal estimates. Where relevant data was not reported by the article, “Not discussed” was  
127 entered into the data extraction form.

128

129 Once data extraction was completed, three columns were added to summarise the type of  
130 outcome being studied: column 1 (“outcome”) was used as a general categorisation of all  
131 outcomes across articles (*e.g.*, the outcome “oestrogen receptor negative (ER-) breast  
132 cancer” would have the value “breast cancer”); column 2 (“outcome info”) reported the  
133 outcome-specific information that distinguished outcomes within categories defined in  
134 column 1 (*e.g.*, column 2 would contain the value “ER- breast cancer” for the same breast  
135 cancer example); and column 3 (“outcome group”) categorised outcomes more generally  
136 than values defined in column 1 (*e.g.*, the breast cancer example would be categorised as  
137 “cancer”). Outcome categories were assigned based on prior biological knowledge and  
138 aimed to collapse the large number of outcomes. Where there were too few outcomes to  
139 make a category, they were grouped into an “other” category.

140

141 *Quality assessment*

142 There is currently no risk of bias tool to assess the quality of MR analyses. Here, the tool  
143 used by Mamluk et al.(2020)<sup>15</sup> was adapted and used for quality assessment of studies  
144 included in the meta-analyses. The quality of each study (MR analysis) within an article  
145 was assessed on a three-point scale (low = 3, medium = 2, high = 1; Extended Data 5) across  
146 12 questions, including the five used by Mamluk et al., (2020)<sup>15</sup>. Additional questions which  
147 aimed to assess instrument selection, sample overlap, sensitivity analyses, descriptive data,  
148 data availability (data missingness), and statistical parameters were included based on a pre-  
149 publication version of the STROBE-MR guidelines. Quality assessment was not used as a  
150 prerequisite for inclusion or exclusion in the meta-analyses. Rather, it was used to  
151 supplement the meta-analyses and aid interpretation, with studies grouped into three  
152 rankings based on their quality assessment score: low (total score 12-19), medium (total  
153 score 20-27) or high quality (total score 28-35).

154

155 *Meta-analysis*

156 Studies were included for meta-analysis if they met a series of rules that ensured the  
157 exposure and outcome were consistent across studies. To be meta-analysed, study methods  
158 had to be compatible, for example, the same MR method(s) and units of measurement. As  
159 sample overlap can induce bias in MR studies<sup>16</sup>, no population overlap between the  
160 different studies that provided data for an outcome being meta-analysed across multiple  
161 MR studies or between the different studies that provided the exposure and outcome data  
162 were permitted within a meta-analysis (**Error! Reference source not found.**). Where there

163 was sample overlap between studies, the study with the larger sample size was retained.  
164 Studies using the same population samples for the exposure data were included as the risk  
165 of bias is low<sup>16</sup>.

166

167 In a fixed-effects meta-analysis, the assumption is that all effect estimates estimate the same  
168 effect. In MR analyses, we assume that studies using the same exposure and outcome will  
169 be estimating the same effect, but that the exposure and outcome is subtly different among  
170 different populations given instrumentation and measurement error. We therefore  
171 consider these to be related effects<sup>17,18</sup>. In an inverse variance weighted fixed-effects model,  
172 a weighted average is calculated as:

173 
$$\text{weighted average} = \frac{\sum y_i (1/SE_i^2)}{\sum (1/SE_i^2)}$$

174 Where,  $y_i$  is the causal effect estimates in the  $i^{th}$  MR study,  $SE_i$  is the standard error of that  
175 estimate, and the summation ( $\Sigma$ ) is across all studies. In a random-effects model,  $SE_i$  is  
176 adjusted to incorporate heterogeneity among study effects ( $\tau^2$ ). In this, a random-effects  
177 model will weight smaller studies more than a fixed-effects model would, as they provide  
178 more information on the distribution of effects as opposed to more information on the  
179 overall effect. This does not mean that random-effects models account for heterogeneity;  
180 random- and fixed-effects models will give identical results when there is no heterogeneity.

181

182 Following this and considerations in the [Cochrane handbook](#), an inverse variance weighted  
183 random-effects model using estimates and standard errors was performed using the meta<sup>19</sup>  
184 package in R and the function metagen. Where standard errors and effect estimates were

185 not available for a study (*e.g.*, confidence intervals (CIs) and odds ratios were available),  
186 these were back-calculated manually. For both binary and continuous outcomes, the  
187 Hartung and Knapp method to adjust CIs to reflect uncertainty in the estimation of  
188 between-study heterogeneity<sup>20,21</sup>, which is recommended for random-effects models<sup>22,23</sup>,  
189 was used where  $\geq 5$  studies were included in the meta-analysis<sup>22</sup>. Between-study variance  
190 was estimated for all meta-analyses using the Paule-Mandel estimator<sup>24</sup>, for which  
191 simulation studies have shown good performance compared to other estimators<sup>25</sup>.

192

193 Forest plots were used to visualise results. For binary outcomes, the relevant summary  
194 method was used for odds ratios, risk ratios, hazard ratios, among others. For continuous  
195 outcomes, the mean difference was used for the underlying summary method. When  
196 presenting results, “increase” and “positive” refer to, for example, a higher BMI or an  
197 increase in the risk of type 2 diabetes; “decrease” and “negative” refer to, for example, a  
198 lower BMI or a decreased risk of type 2 diabetes.

199

## 200 ***Narrative synthesis***

201 A narrative synthesis of all studies not included in the meta-analyses was performed in  
202 order to gain a global picture of reported causal effects. The narrative synthesis summarised  
203 the reported directions of effect estimates across outcome categories, including a summary  
204 of the evidence for selected exposures and outcomes. The outcome categories were used to  
205 guide the synthesis. Given the non-independence of studies and the focus on summarising  
206 directions of effect estimates, the synthesis should be interpreted as an overview and not

207 as definitive evidence for a causal effect. For a complete picture, or to look at specific  
208 exposure-outcome pairs, data extracted from all included studies are available from  
209 Extended Data 3 and can be [browsed online](#).

## 210 Results

### 211 *Literature search and data extraction*

212 A total of 173 articles met the pre-defined inclusion criteria after full text screening (**Error!**  
213 **Reference source not found.**; PDFs for each article available on [GitHub](#)) – articles from  
214 bioRxiv included in data extraction were replaced with their published version if available.  
215 Of the 23 included bioRxiv articles, 18 were published once data extraction began and these  
216 published versions were included instead of the bioRxiv article. One bioRxiv article was  
217 excluded as the published version did not include the MR analysis. The remaining four  
218 bioRxiv articles were included. Most of the 173 articles were published in the past five  
219 years (**Error! Reference source not found.**). Data were extracted for 2,214 studies performed  
220 across the 173 articles (*i.e.*, many articles conducted multiple MR analyses) and one-sample  
221 MR was the predominant analysis performed (**Error! Reference source not found.**). This  
222 included 30 exposures and 659 outcomes. The majority of studies (68%) used BMI as the  
223 exposure (  
224 Table 1). The largest proportion of outcomes were grouped into the metabolic (18%) and  
225 cancer categories (16%) (Table 2). The “other” category included 118 methylation  
226 outcomes, 68 mortality outcomes, and a handful of the following outcomes: age related  
227 macular degeneration, cataract, disease count, hernia, sleep, and physical activity.

228

229 *Table 1 Number and frequency of exposures used across all 2,214 Mendelian randomization analyses*

Exposure	N	%
BMI	1509	68.16
WHR adjusted for BMI	156	7.05
WHR	112	5.06

Birth weight	102	4.61
WC	50	2.26
BF	45	2.03
Fat mass	37	1.67
BMI increasing and WHR decreasing	20	0.90
BMI increasing and WHR increasing	20	0.90
Fat free mass	15	0.68
Obesity	15	0.68
WC adjusted for BMI	14	0.63
Fat percentage	10	0.45
HC	10	0.45
Hepatic fat	10	0.45
Non-fat mass	10	0.45
Sum of skinfolds	10	0.45
Total body fat	10	0.45
Fat mass index	9	0.41
HC adjusted for BMI	9	0.41
Favourable adiposity	7	0.32
Overweight	7	0.32
Lean mass	6	0.27
Body fat mass	5	0.23
Central obesity	4	0.18
Adiponectin	3	0.14
Obesity class 1	3	0.14
Weight	3	0.14
Body non-fat mass	2	0.09
Body fat	1	0.05

BMI = body mass index; WHR = waist hip ratio; WC = waist circumference; HC = hip circumference; BF = body fat percentage.

230

231

232

233 *Table 2 Number and frequency of outcomes within each outcome category across all 2,214 Mendelian randomization*  
234 *analyses*

Outcome group	N	%
Metabolic	404	18.25
Cancer	352	15.90
Respiratory	318	14.36
Cardiovascular	285	12.87
Other	235	10.61
Mental health	127	5.74
Skeletal	95	4.29
Anthropometric	85	3.84
Brain	73	3.30
Hepatic	71	3.21
Social	71	3.21
Renal	34	1.54
Reproductive	19	0.86
Gastrointestinal	17	0.77
Skin	16	0.72
Immune	12	0.54

235

### 236 *Meta-analysis and quality assessment*

237 In total, 66 studies from 34 articles were included in 29 meta-analyses – studies  
238 investigating the effect of adjusted variables (*i.e.*, WHRadjBMI) in two-sample settings  
239 were excluded given recent evidence of biased estimates when using adjusted traits in MR  
240 studies<sup>26</sup>. Most of the 2,214 studies were excluded due to a lack of meta-analysable data  
241 (*e.g.*, only one MR analysis looked at a given exposure-outcome pair). The average  
242 quality assessment score across the 66 studies was 24 (standard deviation (SD) = 2.8; **Error!**  
243 **Reference source not found.**). Only the study of the association between BMI and  
244 haemorrhagic stroke by Dale *et al.*, (2017)<sup>27</sup> was ranked as high quality. All low scoring  
245 studies showed consistent directions of effect with the other studies with which they were



246 meta-analysed. Quality assessment scores for each study are presented alongside the meta-  
247 analysis results (**Error! Reference source not found.** and **Error! Reference source not**  
248 **found.**). The majority of studies included in the meta-analyses used sex-combined data for  
249 the exposure and outcome. As such, we consider meta-analysis results to be the sex-  
250 combined effect of the exposure on the outcome. The exception is for the sex-specific  
251 outcomes endometrial, ovarian, and prostate cancer and polycystic ovary syndrome which  
252 used sex-specific outcome data. For these four outcomes only, we consider the effect on the  
253 outcome to be sex-specific.

254

255 All results are given per SD unit increase. For all binary outcomes, results are given as an  
256 odds ratio (OR) and reflect the OR of the outcome per SD unit increase in the exposure.  
257 For continuous outcomes, results are given as the mean difference (MD) and reflect an  
258 average unit change in the outcome per SD unit increase in the exposure. The term “effect  
259 estimate” is used throughout.

260

261 Of the 20 binary (**Error! Reference source not found.**) and 9 continuous (**Error! Reference**  
262 **source not found.**) outcomes, 5 meta-analyses had negative effect estimates: birthweight on  
263 ER-breast cancer and colon cancer, and BMI on high-density lipoprotein cholesterol (HDL-  
264 C; analysed with SD and mmol/L units) and low-density lipoprotein cholesterol (LDL-C;  
265 mmol/L). 14 of the remaining tests had positive effect estimates with CIs that did not span  
266 the null. The remaining 10 tests had positive effect estimates with CIs that spanned the  
267 null. There was little difference between effect estimates from studies contributing to

268 individual meta-analyses that had a low-quality assessment score and studies with a  
269 medium or high-quality assessment score. One outcome was investigated using more than  
270 one exposure, colorectal cancer with BMI and WHR. There was evidence for an increasing  
271 effect of both measures on colorectal cancer: WHR (OR = 1.48; 95% CI = 1.08–2.03); BMI  
272 (OR = 1.18; 95% CI = 1.01–1.37.

273

274 BMI was the predominant exposure and was found to be associated with an increase in the  
275 risk of all cancers tested (colorectal, endometrial, lung, ovarian, and prostate), CIs crossed  
276 the null only for prostate cancer (OR = 1.08; 95% CI = 0.91–1.28). There was weak evidence  
277 for an association between BMI and ischemic and haemorrhagic stroke, hypertension,  
278 arthritis, and Alzheimer's disease, with effect estimates close to the null and CIs spanning  
279 the null.

280

281 There was evidence of heterogeneity within the included studies, 8 of 20 binary outcomes  
282 and 5 of 9 continuous outcomes had heterogeneity statistics with p-values  $\leq 0.05$ . However,  
283 given no meta-analysis met the requirements for heterogeneity statistics ( $\geq 5$  studies)<sup>28</sup>  
284 these results should be interpreted with caution.

285

### 286 *Narrative synthesis*

287 A total of 2,144 studies were not included in the meta-analyses. A complete summary for  
288 each outcome category is available as Extended Data 6. All extracted data are available from  
289 Extended Data 3 and can be [browsed online](#). Briefly, of the 2,144 studies, 1,343 reported a

290 positive direction of effect and 597 reported a negative direction of effect. The remaining  
291 204 studies either did not report an effect estimate or the effect estimate was null. The  
292 largest number of studies and articles investigated the association between adiposity and  
293 metabolic or cancer outcomes which are summarised here. In this synthesis we discuss  
294 directions of effect across all studies and do not account for sex in this regard.

295

296 For the metabolic category, 380 studies were reported across 51 articles. 89 studies reported  
297 a positive effect estimate and 266 studies reported a negative effect estimate, the remaining  
298 studies did not report an effect estimate. For example, there was weak evidence for an  
299 increasing effect of BMI on cholesterol, but strong evidence for an increasing effect of  
300 WHRadjBMI on cholesterol. Evidence was strongest for outcomes analysed by multiple  
301 studies and articles. For example, there was strong evidence for an increasing effect of BMI,  
302 birth weight, childhood BMI, WHR, WHRadjBMI, and WC on diabetes (type 1, type 2,  
303 and all).

304

305 For the cancer category, 332 studies were reported across 39 articles. Overall, 189 studies  
306 reported a positive effect estimate and 137 studies reported a negative effect estimate; the  
307 remaining studies reported an effect estimate equal to the null: most studies reported CIs  
308 which spanned the null. A total of 31 cancer outcomes were investigated across the 332  
309 studies, with breast cancer the most common, followed by lung, ovarian, and colorectal  
310 cancers. Negative effect estimates were found for cervical (with BMI and WHRadjBMI),  
311 clear cell (with BMI), and gastric (with BMI) cancers. Positive effect estimates were found

312 for Barrett's esophagus (with BMI), colon (with BMI), esophageal (with BMI), lymphoid  
313 (with BMI), meningioma (with BMI, WC, and BF), rectal (with BMI), renal (with BMI,  
314 WHR, and BF), skin (including melanoma; with BMI), stomach and esophageal (with BMI),  
315 and low malignant potential tumours (with BMI). Positive and negative effect estimates  
316 were found for the remaining cancer outcomes, including breast, colorectal, endometrial,  
317 glioma, kidney, lung, multiple myeloma, ovarian, pancreatic, prostate, testicular, and upper  
318 aerodigestive cancers. Broadly, results suggest adiposity increases overall cancer risk and  
319 risk of mortality. However, this risk is modulated by cancer type and subtype.

320 **Discussion**

321 Here, 173 articles and 2,214 MR analyses were reviewed. Meta-analyses and a narrative  
322 synthesis of these studies provide an overview of the causal landscape of adiposity. Broadly,  
323 evidence points to an increasing effect of adiposity on a wide array of outcomes, including  
324 many cancers as well as cardiovascular traits, and type-2 diabetes. It was not possible to  
325 summarise the effect of adiposity on each outcome in the narrative synthesis. Instead,  
326 extracted data from all 2,214 studies are available as Extended Data 5 and via a [data browser](#).  
327 Broadly, results from the meta-analyses were consistent with the narrative synthesis.  
328 However, there was variability within outcomes.

329

330 There were some inconsistencies between evidence from the meta-analyses and narrative  
331 synthesis. For example, there was evidence for an increasing effect of adiposity on  
332 endometrial and colorectal cancer in the meta-analysis, but within the narrative synthesis,  
333 there were studies that reported evidence of an increasing, protective, and null effect of  
334 adiposity on both cancers. This is expected to some degree since in meta-analyses the  
335 sample size is considered, and studies are weighted by this. In contrast, in the narrative  
336 synthesis, only the direction of effect was used to summarise the effect of adiposity.  
337 Additionally, studies included in the meta-analyses were non-overlapping, whereas the  
338 narrative synthesis will have included numerous studies of the same exposure-outcome pair  
339 with overlapping samples. As a result, effects from the same population are likely repeated  
340 in the narrative synthesis, which may have biased the summation of the overall effect of  
341 adiposity.

342

343 Many of the consistent effects observed across the meta-analyses and narrative synthesis  
344 are supported by observational studies, including increased risk of CVD<sup>4</sup> and hypertension<sup>6</sup>.  
345 However, there are some inconsistencies with the observational literature, notably for the  
346 effect of adiposity on haemorrhagic stroke, where evidence for an effect of adiposity was  
347 weak in meta-analysis but is strong in observational analyses<sup>29</sup>. There was also evidence in  
348 the narrative synthesis for an effect of adiposity on a broad number of metabolites which  
349 is also found in the observational literature<sup>6,30</sup>. However, there was weak evidence in the  
350 meta-analyses for a decreasing effect of BMI on HDL-C and an increasing effect on LDL-C  
351 (*e.g.*, the estimate with SD units was positive and had less heterogeneity across the studies  
352 meta-analysed), which is repeatedly found in observational studies<sup>6,30</sup>.

353

354 A particular consideration from this work is the shallowness of the identified exposure-  
355 outcome pairs. That is, many outcomes have been assessed, but these have predominantly  
356 been assessed with BMI as the exposure. Although there is some replication of the results  
357 of the association between BMI and various outcomes, they are concentrated on more  
358 heavily studied diseases such as cancer and CVD. An additional component of this  
359 observation is the use of meta-analyses and biobanks, whereby the same exposure-outcome  
360 association has been assessed using ever larger samples, which include the same  
361 populations. This poses a potential problem for future work, whereby large studies using  
362 meta-GWAS and biobanks, due to their size, are able to capture population structure<sup>31</sup>. If  
363 not controlled within GWASs and MR analyses, this population structure may bias MR

364 analyses and meta-analyses of MR results due to the introduction of genetic confounding  
365 and violation of the second MR assumption.

366

367 Data extraction was based on the STROBE-MR guidelines, which includes information on  
368 interpretability and reproducibility. It was not possible to extract all data from many of the  
369 2,214 studies included in the review. Although some of this data related to reproducibility  
370 guidelines (*e.g.*, software used) a large proportion was related to interpretability (*e.g.*, SNPs  
371 used). This also included data on sex, which was routinely missing or difficult to extract  
372 from both the MR studies and original GWAS publications from which the MR studies  
373 obtained exposure and/or outcome data. This limited the scope of the narrative synthesis  
374 to an overall summary of the direction of effect estimates and did not allow for sex-specific  
375 summaries. As the STROBE-MR guidelines have now been published<sup>14</sup>, it is expected that  
376 the reporting quality of studies will improve. The omission of methodological detail is  
377 unlikely to affect the results of an analysis but does impact on reproducibility and the reuse  
378 of results in meta-analyses such as those presented here.

379

380 Most studies employed similar instrumentation approaches, using a p-value threshold of 5  
381  $\times 10^{-8}$  and a linkage disequilibrium R<sup>2</sup> threshold of 0.0001 (the default for the  
382 TwoSampleMR R package) to identify independent instruments. This has the advantage  
383 that many studies will likely have used the same SNPs for the same exposure. Similarly,  
384 most studies used the same methodologies; however, there was little investigation of non-  
385 linear effects.

386

387 *Strengths and limitations*

388 The majority of the 29 meta-analyses included just two MR analyses; this was primarily a  
389 result of overlapping outcome samples across studies which would ultimately bias results  
390 towards the confounded observational estimate<sup>16</sup>. This overlap suggests replication within  
391 the literature but also the use of meta-GWAS to obtain ever larger populations for MR  
392 analyses. The limited number of analyses included in each meta-analysis (*i.e.*, < 5 studies)  
393 prevents meaningful interpretation of heterogeneity statistics<sup>28</sup> and prevented the  
394 assessment of publication bias.

395

396 Given the incomplete and often poor reporting of MR analyses, results here should be  
397 interpreted cautiously. Studies were excluded from meta-analysis if there was overlap  
398 between the outcome data between studies or between the exposure data and outcome data  
399 between studies. However, it is possible that this was not completely accurate given that  
400 not all studies reported the cohorts used in their analyses. Additional limitations of MR  
401 analyses, including homogeneity and monotonicity, may be especially important in meta-  
402 analysis results given effects among different populations may not be homogeneous (*i.e.*,  
403 the effect of the IV or exposure is not the same for all populations) or monotonic (*i.e.*, the  
404 effect of the IV on the exposure is differential among populations).

405



406 *Conclusions*

407 Adiposity is shown to exert a predominantly increasing effect on numerous outcomes  
408 including many cancers, cardiovascular outcomes, and metabolic traits. Results here are  
409 broadly consistent with the observational literature and provide corroborative evidence for  
410 associations with several traits. However, these results are not definitive and should instead  
411 be used as a guide for future investigations aiming to triangulate evidence of association<sup>7</sup>.  
412 There is a need to update this work, especially considering the large body of work  
413 conducted during the SARS-CoV-2/COVID-19 pandemic, and it is hoped this will become  
414 easier as the quality of studies improves with the adoption of the STROBE-MR guidelines.  
415

416 Data availability

417 *Underlying data*

418 All data, scripts, results, and figures are available on [GitHub \(10.5281/zenodo.7377406\)](https://github.com/10.5281/zenodo.7377406). All  
419 data obtained from the data extraction process can be accessed via Extended Data 3 and can  
420 be [searchable online](#).

421

422 *Extended data*

423 All Extended Data, including the preregistration document and PRISMA checklists, are  
424 available from Zenodo: [10.5281/zenodo.7377442](https://zenodo.org/record/10.5281/zenodo.7377442). Extended data includes:

425

- 426 1. PROSPERO preregistration document
- 427 2. Search strategy
- 428 3. Data extraction manual, data extraction form with raw data, and formatted  
429 extracted data
- 430 4. Formatted results from meta-analyses
- 431 5. Quality assessment tool and results
- 432 6. Narrative synthesis of all non-meta-analysed studies
- 433 7. PRISMA checklists
- 434 8. Letter from editor of IJE and response to reviewer comments
- 435 9. PRISMA flowchart

436

437 Data are available under the terms of the [Creative Commons Zero “No rights reserved” data](#)

438 [waiver](#) (CC0 1.0 Public domain dedication).

439

440 *Author contributions*

441 MAL: conceptualization, data curation, formal analysis, investigation, methodology,  
442 project administration, software, supervision, validation, visualization, writing (original  
443 draft preparation), writing (review & editing)

444

445 CH: data curation, investigation, validation, writing (review & editing)

446

447 LJM: data curation, methodology, writing (review & editing)

448

449 NM: data curation, writing (review & editing)

450

451 TB: data curation, writing (review & editing)

452

453 WW: data curation, writing (review & editing)

454

455 SF: data curation, writing (review & editing)

456

457 KHW: resources, data curation, supervision, writing (review & editing)

458

459 LJC: resources, supervision, writing (review & editing)

460

461 NJT: resources, funding acquisition, supervision, writing (review & editing)



463 Competing interests

464 No competing interests were disclosed

465

466 Funding

467 This work was supported by the Wellcome Trust through a Wellcome Trust Investigator  
468 award to NJT (202802/Z/16/Z). MAL is funded by a Medical Research Council GW4  
469 studentship (grant number: MR/R502340/1). NJT is a Wellcome Trust Investigator  
470 (202802/Z/16/Z), is the PI of the Avon Longitudinal Study of Parents and Children (MRC  
471 & WT 217065/Z/19/Z), is supported by the University of Bristol NIHR Biomedical  
472 Research Centre (BRC-1215-2001), the MRC Integrative Epidemiology Unit  
473 (MC\_UU\_00011/1) and works within the CRUK Integrative Cancer Epidemiology  
474 Programme (C18281/A29019). L.J.C. is supported by N.J.T.'s Wellcome Investigator  
475 Award (202802/Z/16/Z). All authors work in the MRC Integrative Epidemiology Unit at  
476 the University of Bristol, which is supported by the Medical Research Council (grant  
477 numbers: MC\_UU\_00011/1-7) and the University of Bristol. LAM is supported by an  
478 NIHR Doctoral Research Fellowship (DRF-2018-11-ST2-048). The views expressed in this  
479 article are those of the authors and do not necessarily represent those of the NHS, the  
480 NIHR, or the Department of Health and Social Care.

481

482 This research was funded in whole, or in part, by the Wellcome Trust [202802/Z/16/Z,  
483 217065/Z/19/Z]. For the purpose of Open Access, the author has applied a CC BY public  
484 copyright licence to any Author Accepted Manuscript version arising from this submission.

485

486 Acknowledgements

487 This work is based on Chapter 2 of the PhD thesis of the first author Matthew A Lee,

488 available from the [University of Bristol](#).

489

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- 564
- 565

566 **Figures and tables**

567

568 *Figure 1 Inclusion criteria for meta-analysis: flowchart. Mendelian randomization (MR) analyses were included in meta-*  
569 *analyses if they met the conditions set out in the flowchart with regards to sample overlap. \* = MR analyses had to use*  
570 *the same exposure and the same outcome to be compatible, e.g., for the exposure, body mass index (BMI) could not be*  
571 *meta-analysed with any other exposure that was not BMI. This also applies to outcomes, e.g., the outcome oestrogen*  
572 *receptor negative (ER-) breast cancer could not be meta-analysed with breast cancer, it could only be meta-analysed with*  
573 *ER- breast cancer.*

574

575 *Figure 2 PRISMA flowchart. N gives the number of articles at each stage. MR = Mendelian randomization.*

576

577 *Figure 3 Distribution of publication year and average exposure and outcome sample sizes across included studies up to*  
578 *the search date of February 2019. The number of articles included per year is given on the left Y axis; the right Y axis*  
579 *gives the average sample size for exposure (grey) and outcome (red) for each year. Outcome cases and controls were*  
580 *summed within analyses for binary outcomes.*

581

582 *Figure 4 Distribution of study design across 173 included articles. The Y axis gives the MR study design and the X axis*  
583 *gives the number of studies for that study design. The majority of the 173 included articles reported more than one*  
584 *Mendelian randomization (MR) analysis. Where a study performed a bi-directional MR analysis and adiposity was the*  
585 *secondary analysis (i.e., to check for reverse causation), this was recorded as a bi-directional MR analysis. One-sample*  
586 *and two-sample MR meta-analysis indicates that the meta-analysis included MR analyses that were both one- and two-*  
587 *sample designs. Generalized summary data-based MR allows for, and models, correlated SNPs within the instrument.*  
588 *Factorial MR is analogous to a factorial randomized controlled trial, whereby individuals are grouped using genetic scores*  
589 *(generally in a 2 x 2 approach). An MR-PheWAS is the investigation of a single trait on many, potentially hundreds, of*  
590 *outcomes. Direct G-O refers to an MR analysis which used instruments from a single locus, e.g., the FTO locus.*

591

592 *Figure 5 Quality assessment: distribution of quality assessment scores for studies included in the meta-analyses. "High"*  
593 *indicates a study scored highly; "low" indicates a study scored poorly. QA = quality assessment score.*

594

595 *Figure 6 Meta-analysis: effect estimates and 95% confidence intervals for binary outcomes. Forest plot shows effect*  
596 *estimates and 95% confidence intervals (CIs) from a meta-analysis of 22 different exposure-outcome pairs. Mendelian*  
597 *randomization analyses included based on criteria in **Error! Reference source not found.** P-values are given for the*  
598 *heterogeneity statistics. QA = quality assessment score; OR = odds ratio. Available on [GitHub](#). Forest plots of individual*  
599 *meta-analyses are also available on [GitHub](#).*

600

601 *Figure 7 Meta-analysis: effect estimates and 95% confidence intervals for continuous outcomes. Forest plot shows effect*  
602 *estimates and 95% confidence intervals (CIs) from a meta-analysis of 9 different exposure-outcome pairs. Mendelian*  
603 *randomization analyses included based on criteria in **Error! Reference source not found.** P-values are given for the*  
604 *heterogeneity statistics. QA = quality assessment score; OR = odds ratio. Available on [GitHub](#). Forest plots of individual*  
605 *meta-analyses are also available on [GitHub](#).*

606

607

608 *Table 3 Number and frequency of exposures used across all 2,214 Mendelian randomization analyses*

609

610 *Table 4 Number and frequency of outcomes within each outcome category across all 2,214 Mendelian randomization*  
611 *analyses*

612