Weight loss interventions on health-related quality of life in those with moderate to severe obesity: Findings from an individual patient data meta-analysis of randomized trials

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Funding information
NIHR Oxford Biomedical Research Centre and Applied Research Collaboration

Summary
The relationship between BMI and health-related quality of life (HRQoL) critically affects regulatory approval of interventions for weight loss, but evidence of the association is inconsistent. A higher standard of evidence than that available was sought with an IPD meta-analysis of 10,884 people enrolled in five randomized controlled trials of intentional weight loss interventions. Cross-sectional and longitudinal associations of BMI and HRQoL were estimated in mixed effects models specifying a latent variable for HRQoL. Spline regressions captured nonlinear associations across the range of BMI. In cross-sectional spline regressions, BMI was not associated with HRQoL for people with a BMI < 30 kg/m² but was for those with a higher BMI. In longitudinal spline regressions, decreases in BMI were positively associated with HRQoL for people with a BMI ≥ 25 kg/m². The impact of change in BMI was larger for people with higher BMIs than for those with BMIs under 30 kg/m². Lower BMI and decreases in BMI were related to higher HRQoL for people living with obesity but not in the population without excess weight. HRQoL gains from weight loss are greater for more severe obesity. Commissioners should use these estimates for future decision making.

KEYWORDS
commissioning, health-related quality of life, IPD meta-analysis, weight loss

1 | INTRODUCTION

Excess weight is associated with substantial morbidity and premature mortality.¹ Excess weight reduces health-related quality of life (HRQoL)—that is, an individual’s or a group’s perceived physical and mental health over time—through effects on incidence of weight-related disease but may also do so directly, compromising daily functioning through difficulty in performing everyday tasks and reducing mental well-being.²,³ Interventions aiming at weight loss have been shown to reduce the incidence of diabetes and premature mortality,⁴,⁵ but the effect on HRQoL is uncertain.

Systematic reviews and meta-analyses indicate several issues with extant evidence on the relationship between BMI and HRQoL.² Within-study results are not always robust across different indicators of HRQoL.⁶ There is some, though limited, evidence that the relationship between BMI and HRQoL is not linear.⁷,⁸ Studies in specific patient groups may not apply to the general population of people with overweight. There are concerns that weight loss attempts may impair mental health.⁹

Paul Aveyard and Susan A. Jebb are of equal contribution.

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Received: 30 March 2021 | Revised: 15 June 2021 | Accepted: 15 June 2021
DOI: 10.1111/obr.13317

Obesity Reviews. 2021;22:e13317.
https://doi.org/10.1111/obr.13317
Across the world, health economic appraisals of behavioral interventions, pharmacotherapeutic interventions, and bariatric surgery have estimated the impact of the intervention on quality of life by assuming that cross-sectional differences between people of different BMIs represent the effect of changing weight on quality of life. Studies have used estimates that differ markedly. Different values could alter decisions on whether to commission these interventions. In the United Kingdom, recent appraisal of liraglutide by the National Institute for Health and Care Excellence (NICE) used values from a cross-sectional, observational study. Here, a nonlinear function of BMI was specified. HRQoL, expressed in utility, increased with BMI up to an inflection point (around BMI = 25 kg/m²); HRQoL declined thereafter. This is in stark contrast to prior approaches in the United Kingdom and internationally that have assumed a single value across the range of BMI. Another issue is that gains in HRQoL from weight loss are often assumed to be sustained, which may not be the case, particularly after nonsurgical interventions. More robust estimates of the HRQoL-BMI relationship and the sustainability over time would enable consistent commissioning decisions.

In this paper, we estimate the association between BMI and HRQoL using longitudinal data from five large RCTs of behavioral weight loss interventions in an individual participant data (IPD) meta-analysis, where weight loss can be assumed to be intentional and not arising from disease. We assess whether the association varied over the distribution of BMI and whether the strength of association was different for the physical and mental domains of HRQoL. The latter in particular is of interest given the lack of existing evidence on this issue.

2 METHODS

2.1 Trial identification

Studies were identified using existing systematic reviews in obesity, reference mining of systematic reviews, and consultation with experts in the field.

2.2 Trial eligibility

(1) Adults (18 years or older) with overweight or obesity at baseline (BMI 25 kg/m² or above) and enrolled in a behavioral weight loss trial, indicating intention to lose weight. For trials that used behavioral and pharmacotherapeutic arms, only data from the behavioral arms were analyzed. Pharmacotherapeutic trials were excluded to avoid any additional impact on individuals’ quality of life, for example, through side-effects. Surgical trials were excluded due to the higher weight of patients undergoing surgery, the substantially larger reduction associated with the intervention and potential for other effects on quality of life not directly related to weight loss. (2) Mean change in weight in the intervention groups ≥ 2 kg. (3) The main outcomes, participants’ BMI and HRQoL, collected at least twice. (4) Trials of more than 1,000 participants were enrolled to ensure that each trial has at least some bearing on the overall relationship of interest. Details of the five trials included—Look AHEAD, TOHP, DPP, WRAP, and DioGENES—are presented below and in detail elsewhere.

1. Diets with High or Low Protein Content and Glycemic Index for Weight-Loss Maintenance (DioGENES)

The population studied was overweight and obese adults in EU countries that had recently lost at least 8% of their bodyweight. A total of 1209 adults participated in the trial. Interventions were ad libitum diets in a two-by-two factorial design (low/high protein, low/high glycemic index); the control was a diet based on countries’ general guidance without reference to glycemic index. The outcome was weight regain. The intervention lasted for a 26-week period; quality of life was collected up to this point. The HRQoL indicator used the obesity-specific Impact of Weight on Quality Of Life (IWQOL).

2. Diabetes Prevention Programme (DPP)

The population studied was adults in the United States with elevated fasting and post-load plasma glucose. A total of 3234 adults were enrolled. Interventions were a weight loss-focused lifestyle intervention and metformin (we did not include this arm—see eligibility criteria); the control was a placebo. The outcome was the incidence of diabetes. Mean follow-up was 2.8 years. The HRQoL indicator used was the SF-36.

3. Look AHEAD

The population studied was adults in the United States being between 55 and 76 years of age, being diagnosed with type II diabetes, and being overweight. A total of 5145 patients participated in the trial. Interventions were intensive lifestyle interventions (increased physical activity and reduced calorie intake); the control was diabetes support and education. Outcomes were adverse effects including death and AMI, stroke, or angina. Mean follow-up was 9.6 years. HRQoL indicators included SF-36, feelings thermometer, HUI2, and HUI3.

4. Trials of Hypertension Prevention (TOHP)

The population studied was adults in the United States being between 30 and 54 years of age, with diastolic blood pressure between 80 and 89. A total of 2182 patients participated in the trial. Interventions were lifestyle interventions (weight reduction, sodium reduction, and stress management); the control was non-intervention. In addition, four nutritional supplements were compared, double-blinded, to a placebo. Outcomes were changes in blood pressure. Follow-up was 18 months. The HRQoL indicator used was the general well-being scale.
were developed. First, HRQoL was regressed on BMI, the group models. Mixed effects models, based on a pre-registered analysis plan, were specified with the latent variable for HRQoL as the dependent variable. Appendix B presents the rationale for this and presents the measurement equations related HRQoL, as an independent variable, to the various indicators of HRQoL across the trials, each of which was separately treated as a dependent variable. Structural equations were specified with the latent variable for HRQoL as the dependent variable. Appendix B presents the rationale for this and presents the models. Mixed effects models, based on a pre-registered analysis plan, were developed. First, HRQoL was regressed on BMI, the group (within-individual) mean of BMI, individual characteristics, trial fixed effects, and time-from-baseline fixed effects. (A model with intervention arm fixed effects was tested, but the main coefficient of interest was consistent; the reported specification was retained to make use of data of all individuals in all arms, all of whose BMI/HRQoL varied.) A random effect for individuals was also specified. LookAHEAD had longer follow up than all of the other trials. We therefore specified time fixed effects only for time periods in which multiple trials observed participants, to avoid attributing time series HRQoL variation in Look AHEAD to other trials. Second, a spline regression was estimated. The range of BMI was partitioned into five regions, each corresponding to one of five BMI categories: healthy weight, overweight, obesity category I, obesity category II, and obesity category III (underweight was omitted as there were no underweight participants enrolled in these trials). We examined the HRQoL-BMI relationship not only at different starting levels of BMI but also at different starting HRQoL levels (see Appendix H). In cross-sectional analyses, all available observations of all individuals in all time periods were analyzed. Next, two similar regressions were estimated, but here, HRQoL was regressed on period-to-period BMI change to examine the relationship between HRQoL and longitudinal variation in BMI.

2.5 Revisiting previous commissioning decisions

Our fitted model was used to repeat the cost-effectiveness of orlistat that informed NICE commissioning using our updated HRQoL-BMI estimate. The VAS scale was used to derive utility as per the original study. All other metrics were taken from the original paper and held constant.

3 RESULTS

Levels of missing HRQoL and BMI data varied across trials (Appendix E). An initial imputation exercise was conducted on each of the data sets separately to gauge the impact of missing data on the estimated relationship of interest. In all cases, the multiply imputed regression results were very similar to those without imputation (Appendix E).

3.1 Descriptive statistics

After removing observations for which either BMI or HRQoL were missing, 58,723 observations of 10,884 individuals were available. The largest trial was Look AHEAD (n = 4900; 45%), followed by TOHP (n = 2172; 20%), DPP (n = 1750; 16%), WRAP (n = 1241; 11%), and DioGENES (n = 821; 8%).

Characteristics of individuals at baseline are presented in Table 1. A total of 8881 individuals were analyzed at baseline. For DPP, data were available at baseline, but only in an aggregated form, which is not compatible with this analysis. Mean BMI at baseline was 33.3 kg/m². There were slightly more females than males (53%) with a mean age of 53 years. Individuals were predominantly white (76%) with around 13% black; this is broadly in line with census data from the trials’ countries.

3.2 Association of HRQoL and its indicators

The associations between HRQoL and all its indicators (SF-36 pcs, SF-36 mcs, EQ-5D, etc.) were positive and statistically significantly different from zero in the linear model and spline regressions (Table 2). Physical health quality of life (SF-36 pcs) had a stronger association with HRQoL than mental health quality of life (SF-36 mcs). In the BMI change (delta) models, neither obesity-specific quality of life (IWQOL) nor mental health quality of life (SF-36 mcs) were related to HRQoL. All other HRQoL indicators were significantly related to HRQoL. 

2.4 Statistical analyses

HRQoL was treated as a latent variable within a system of equations. Measurement equations related HRQoL, as an independent variable, to the various indicators of HRQoL across the trials, each of which was separately treated as a dependent variable. Structural equations were specified with the latent variable for HRQoL as the dependent variable. Appendix B presents the rationale for this and presents the models. Mixed effects models, based on a pre-registered analysis plan, were developed. First, HRQoL was regressed on BMI, the group (within-individual) mean of BMI, individual characteristics, trial fixed effects, and time-from-baseline fixed effects. (A model with intervention arm fixed effects was tested, but the main coefficient of interest was consistent; the reported specification was retained to make use of data of all individuals in all arms, all of whose BMI/HRQoL varied.) A random effect for individuals was also specified. Look AHEAD had longer follow up than all of the other trials. We therefore specified time fixed effects only for time periods in which multiple trials observed participants, to avoid attributing time series HRQoL variation in Look AHEAD to other trials. Second, a spline regression was estimated. The range of BMI was partitioned into five regions, each corresponding to one of five BMI categories: healthy weight, overweight, obesity category I, obesity category II, and obesity category III (underweight was omitted as there were no underweight participants enrolled in these trials). We examined the HRQoL-BMI relationship not only at different starting levels of BMI but also at different starting HRQoL levels (see Appendix H). In cross-sectional analyses, all available observations of all individuals in all time periods were analyzed. Next, two similar regressions were estimated, but here, HRQoL was regressed on period-to-period BMI change to examine the relationship between HRQoL and longitudinal variation in BMI.

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3.3 | Cross-sectional associations of HRQoL and BMI

In a linear model, BMI and HRQoL were negatively associated. A one-unit lower BMI was associated with a 0.13-standard deviation unit higher HRQoL (BMI = −0.13; 95% CI: −0.14 to −0.12) (Table 3). In the spline regression, there was no evidence of association between HRQoL and BMI when BMI was below 25 kg/m². At higher BMI, there was a significant inverse association. BMI in the range 25–29.9 kg/m² had the smallest association with HRQoL. A stronger association was observed when BMI was 35–39.9 kg/m² (BMI: 35–39.9 = −1.44; 95% CI: −1.70 to −1.19). The strongest association was observed when BMI ≥ 40 kg/m² (BMI: ≥40 = −2.95; 95% CI: −3.39 to −2.51).

Taking the estimate from the linear model, one-unit lower in BMI would relate to higher HRQoL on its various indicators (listing only statistically significant associations): SF-36 pcs 0.38; SF-36 mcs 0.21; Feelings Thermometer 0.64; IWQoL 1.35; EQ-5D 0.01; EQVAS 0.01; well-being 0.52.

3.4 | Associations of change in BMI with HRQoL

In a model examining BMI change and HRQoL, there was a negative association. A one unit decrease in BMI was associated with a 0.09-standard deviation unit higher HRQoL (change in BMI = −0.09; 95% CI: −0.10 to −0.08) (Table 4). In a delta spline regression, there was no evidence of association between HRQoL and changes in BMI when BMI was below 25. At higher BMI, there were significant inverse associations. The association was modest in BMI range 25–29.9 kg/m² at −0.09 (95% CI: −0.13 to −0.04) and was progressively stronger in each 5-point higher grouping (Table 4). Above a BMI of 40 kg/m², a one unit BMI increase was associated with a −0.15 lower HRQoL (95% CI: −0.23 to −0.07).

Here, a one-unit loss in BMI would relate to higher HRQoL on its various indicators (listing only statistically significant associations): SF-36 pcs 0.43; Feelings Thermometer 0.62; EQ-5D 0.01; EQVAS 0.01; well-being 0.35.

3.5 | Reconciling past commissioning decisions with updated BMI-HRQoL estimates

To demonstrate an application of our results, we revisit a cost-effectiveness evaluation of orlistat. The previous cost (£) per quality-adjusted life year (QALY) was £24,430.50 (Table 5). Two results from this study were then applied to the same calculation: cross-sectional results from the linear regression (cost per QALY: £80,499.86) and results from the delta regression (cost per QALY: £60,517.02). Hence, using the results of our study may have a sizable impact on whether weight reduction interventions such as orlistat are deemed cost-effective, particularly in countries such as England where thresholds of £20,000–£30,000 applied by decision making bodies such as NICE.

3.6 | Nonlinear HRQoL and QALYs

Nonlinear HRQoL change from spline regressions was converted into QALYs to demonstrate the heterogeneity of HRQoL across the range of BMI; QALYs ranged from 0 to 0.427 (Table 6). In both cases, the mean change in QALYs was different to that in each of the categories underscoring the importance of this heterogeneity. Stark differences between the linear model and the delta model reinforce the difference between BMI change and cross-sectional differences in BMI: cross-sectional models may be overestimating QALY gains.
In a cross-sectional analysis of individual participant data from five intentional weight loss trials, HRQoL was negatively related to BMI, primarily because of an inverse association in those with BMI > 30, with no evidence of an association in the BMI range under 30 kg/m². In longitudinal analysis, HRQoL was negatively related to change in BMI in people with a BMI > 25 kg/m². The coefficients in the cross-sectional analyses for people with a high BMI were larger than those for change in BMI. The mean of the HRQoL indicators is close to those at the population mean. However, we were able to exploit BMI variation to examine how the HRQoL-BMI relationship varied across the range of BMI.

We used IPD from large randomized controlled trials in several countries to perform a meta-analysis to provide a robust synthesis of the available evidence. We were able to exploit both the cross-sectional and longitudinal aspects to provide robust evidence and new insights into the relationship between BMI and HRQoL. A natural limitation of the pooled data is that variables are not collected consistently across trials. We sought to overcome that and exploit the precision of pooled data through the use of latent variable modelling, but if the association between quality of life and each measure genuinely differs, this will only be partially successful. Incident or prevalent disease related to BMI could partly be responsible for the differences by BMI, but given the relatively short follow-ups, is less likely to cloud the data on change in BMI. A potential limitation is that one trial, LookAHEAD, provided 45% of the total participants and with the longest follow up. However, we found associations across all trials, and the results for each study were similar (Appendix E). It is not known whether these results can be generalized to other weight-loss interventions. A further issue is that we cannot rule out confounding if actions which resulted in weight loss directly impacted on HRQoL and not only though changes in BMI. The direction and magnitude of these effects are unknown. This would not be the case for control arm individuals (a model only on control arm individuals in Appendix G shows consistent results). However, beyond any specific effect caused by participation in a trial, it reflects what happens when people lose weight—in a world of other competing effects on HRQoL. Finally, direct comparison across the HRQoL indicators is inappropriate because they are all attempting to measure HRQoL in different ways, but our use of latent variable analysis overcame this to some extent. Indeed, we see our approach as a pragmatic solution to the vexing issue of modelling different HRQoL indicators together. However, the latent variable is not without potential theoretical limitations. We have assumed within this approach that HRQoL is causing the indicators of it, but the opposite is of course possible. The latent variable is ultimately capturing shared variation among the separate HRQoL indicators; whether or not this constitutes a true HRQoL, if such a singular thing exists, is open to question. We reiterate that, aside from the EQVAS, HRQoL scales are analyzed in their raw form without having preference tariffs applied, and should be understood as such.
While our findings generally confirm the direction of effect in previous estimates, we provide new data on how BMI change appears to influence HRQoL, and importantly, we show that the effect of this depends upon starting BMI. The association is stronger for physical HRQoL than mental HRQoL. Prior evidence of the association between mental HRQoL and BMI is mixed, including mainly negative results, but some reports of positive associations or non-significant estimates. One meta-analysis reported higher mental HRQoL in overweight than for healthy weight. These inconsistent findings may be because the magnitude of the association is

### TABLE 3  Cross-sectional estimates of associations between 1 kg/m² difference in BMI and standard deviation units of HRQoL from the structural equations from the linear model and spline regression

|          | Linear model |       |       |        | Spline regression |       |       |        |
|----------|--------------|-------|-------|--------|------------------|-------|-------|--------|
|          | Est 95% CI   |       |       | p value | Est 95% CI      |       |       | p value |
| BMI: 18.5–24.9 | −0.13 (−0.139 to −0.124) |       |       | <0.01  | 0.00             |       |       |        |
| BMI: 25–29.9   |       |       |       |        | 0.00             |       |       |        |
| BMI: 30–34.9   | −0.36 (−0.59 to −0.139) |       |       | <0.01  | −1.16 (−1.71 to −0.6) |       |       | <0.01  |
| BMI: 35–39.9   |       |       |       |        | −2.42 (−3.51 to −1.338) |       |       | <0.01  |
| BMI: ≥40       |       |       |       |        | 2.42 (3.51 to 1.338) |       |       | <0.01  |

Abbreviations: Est, estimate; 95% CI, 95% confidence interval.
Note: HRQoL was in turn related to each of its indicators (see Table 2 for ranges of individual HRQoL indicators).

### TABLE 4  Longitudinal estimates of association between changes in BMI and standard deviation units of HRQoL from the structural equations from the delta model and delta spline regression

|          | Delta model |       |       |        | Delta spline regression |       |       |        |
|----------|-------------|-------|-------|--------|-------------------------|-------|-------|--------|
|          | Est 95% CI   |       |       | p value | Est 95% CI              |       |       | p value |
| Change in BMI | −0.087848 (−0.099 to −0.075) |       |       | <0.01  | 0.00                    |       |       |        |
| Change in BMI: 18.5–24.9 |       |       |       |        | −0.08522 (−0.131 to −0.039) |       |       | <0.01  |
| Change in BMI: 25–29.9   |       |       |       |        | −0.1048 (−0.162 to −0.046) |       |       | <0.01  |
| Change in BMI: 30–34.9   |       |       |       |        | −0.12335 (−0.193 to −0.052) |       |       | <0.01  |
| Change in BMI: 35–39.9   |       |       |       |        | −0.1524 (−0.231 to −0.073) |       |       | <0.01  |

Abbreviations: Est, estimate; 95% CI, 95% confidence interval.
Note: HRQoL was in turn related to each of its indicators (see Table 2 for ranges of individual HRQoL indicators).

### TABLE 5  NICE cost-effectiveness of orlistat using the original value and using our estimates

|          | Utility gain | BMI change | Change in QALYs | QALY change in the trial arm | QALYs/100 | Cost/100 | Cost per QALY |
|----------|--------------|------------|-----------------|-------------------------------|-----------|----------|---------------|
| Foxcroft orlistat | 0.017 | 6.862 | 0.117 | 1.493 | 0.927 | 22744.8 | 24,430.50 |
| Buckell et al. static orlistat | 0.005 | 6.862 | 0.036 | 0.455 | 0.283 | 22744.8 | 80,499.86 |
| Buckell et al. delta orlistat | 0.007 | 6.862 | 0.047 | 0.605 | 0.376 | 22744.8 | 60,517.02 |
| Foxcroft Placebo | 0.017 | 6.282 | 0.107 | 0.566 |       |         |               |
| Buckell et al. static Placebo | 0.005 | 6.282 | 0.033 | 0.172 |       |         |               |
| Buckell et al. delta Placebo | 0.007 | 6.282 | 0.043 | 0.229 |       |         |               |

Abbreviation: QALY, quality adjusted life year.
Note: “Utility gain” is the gain in utility from a one unit decrease in BMI. This is derived from the EQVAS measure which is converted to a utility score based on Hakim et al.13 “BMI change” is the total BMI change in the trial arm. “Change in QALYs” multiplies the first two columns. “QALY change in the trial arm” computes the QALY changes per 100 respondents in each trial arm. “QALYs/100” takes the difference in QALY changes between treatment and control. “Cost/100” is the cost of the treatment per 100 respondents. “Cost per QALY” is the cost per QALY of the intervention from the original study and using our revised estimates. Figures that are not computed in this paper can be found in the original study.12
small, and many studies are underpowered to detect effects. We found no evidence of any adverse effects of intentional weight loss on mental health, even after weight regain, providing some reassurance to those expressing concerns. Understanding HRQoL is key for commissioning decisions about treatment interventions and so critical to patient care. The present study offers the highest quality evidence to date on the relationship between BMI and health-related quality of life in the context of behavioral interventions. In updating prior cost-effectiveness calculations, a different commissioning decision would have been made if these results had been used (though we recognize that our results are derived from behavioral interventions and applied to a pharmacotherapeutic intervention). The present study highlights the stronger relationship between BMI and HRQoL for people with BMI ≥ 30 kg/m², where treatments are most often targeted. Commissioners in the United Kingdom have previously used an estimate of HRQoL-BMI at the sample mean, disregarding the heterogeneity across the range of BMI. This implies gains in HRQoL used to determine the cost-effectiveness of interventions will be underestimated. This was applied in the case of orlistat when it was considered by NICE. For recent appraisals, NICE have used estimates in which the value of HRQoL-BMI varies over BMI. However, these values rely on cross-sectional, observational evidence which we show greatly overestimates the change observed with intervention as demonstrated in QALY conversions of our HRQoL estimates. Furthermore, HRQoL gains in appraisals have assumed to be sustained; our results indicate that this is not the case (Appendix D). Our results, which provide estimates specific to people with a BMI > 30 kg/m² and examine the change with behavioral interventions, are likely to provide a more appropriate estimate, especially since initial states of HRQoL vary between categories of BMI. Our results can be used for commissioning decisions involving any of the HRQoL indicators because we measured their association with HRQoL and in turn its association with BMI. Without a robust, well-accepted relationship, there is potential for inconsistencies to emerge in commissioning determinations. Similar analyses are warranted with regard to decisions on pharmacological agents and surgical interventions for weight management.

ACKNOWLEDGMENTS

We thank Frauke Becker for providing STATA code for processing trials' data. We thank attendees at Health Economists’ Study Group meeting and CERGAS at Bocconi University for useful comments when discussed. This work was supported by the NIHR Oxford Biomedical Research. PA and SAJ are NIHR senior investigators and funded by the NIHR Oxford Biomedical Research Centre and Applied Research Collaboration.

The Diabetes Prevention Program (DPP) was conducted by the DPP Research Group and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the General Clinical Research Center Program, the National Institute of Child Health and Human Development (NICHD), the National Institute on Aging (NIA), the Office of Research on Women's Health, the Office of Research on Minority Health, the Centers for Disease Control and Prevention (CDC), and the American Diabetes Association. The data (and samples) from the DPP were supplied by the NIDDK Central Repositories. This manuscript was not prepared under the auspices of the DPP and does not represent analyses or conclusions of the DPP Research Group, the NIDDK Central Repositories, or the NIH.

Look AHEAD was conducted by the Look AHEAD Research Group and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Nursing Research (NINR); the National Institute of Minority Health and Health Disparities (NIMHD); the Office of Research on Women's Health (ORWH); and the Centers for Disease Control and Prevention (CDC). The data (and samples) from Look AHEAD were supplied by the NIDDK Central Repositories. This manuscript was not prepared under the auspices of the Look AHEAD and does not represent analyses or conclusions of the Look AHEAD Research Group, the NIDDK Central Repositories, or the NIH.

This manuscript was prepared using TOHP Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the TOHP or the NHLBI.
This manuscript was prepared using DioGENES Research Materials obtained from the DioGENES trial and does not necessarily reflect the opinions or views of the DioGENES trial. This manuscript was prepared using WRAP Research Materials obtained from the WRAP trial and does not necessarily reflect the opinions or views of the WRAP trial.

CONFLICT OF INTEREST
There are no conflicts of interest to declare.

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ENDNOTE
* See the database of mapping studies, Dakin et al. (2018).

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How to cite this article: Buckell J, Mei XW, Clarke P, Aveyard P, Jebb SA. Weight loss interventions on health-related quality of life in those with moderate to severe obesity: Findings from an individual patient data meta-analysis of randomized trials. Obesity Reviews. 2021;22(11):e13317. https://doi.org/10.1111/obr.13317
APPENDIX A: HRQoL OUTCOMES

Main outcome(s): The main outcome of interest was HRQoL. Across the trials, various HRQoL indicators were used. Each trial included required at least one of the following indicators. Obesity-specific minimally clinically important distances (MCIDs) are reported (Warkentin et al., 2014) and more general MCIDs where obesity-specific values are not available (Zhang et al., 2021).

i. Short Form-36 (SF-36, version 2; Brazier et al., 2002). General population-based quality of life measure. Comprises both physical (pcs) and mental (mcs) health. Physical health is measured using 21 items across four domains. Mental health is measured using 14 items across four domains. Items are summarized into overall pcs and mcs scores. These are t scores with a mean of 50 and standard deviation of 10, based on the U.S. population. The MCID for both the pcs and the mcs is 5.

ii. Short-Form Impact of Weight on Quality Of Life (IWQOL-Lite; Kolotkin et al., 2002). An obesity-specific measure of HRQoL. There are 31 items over five scales (physical function, self-esteem, sexual life, public distress, and work). Items are summarized into overall scores ranging from 0 to 100. The MCID is 12.

iii. EuroQol Five Dimension (EQ-5D; EuroQol, 1990). A general population, preference-based health status measure. It comprises five dimensions of health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Items are summarized into overall scores ranging from 0 to 1. The MCID is 0.03.

iv. EuroQol Visual Analogue Scale (EQVAS). A vertical scale ranging from 0 to 100. Zero is labelled “the worst imaginable health state” or “the worst health you can imagine.” and 100 is labelled “the best imaginable health state” or “the best health state you can imagine.” The MCID is 10.

v. Feeling thermometer. A visual analogue scale of 0 to 100 that allows individuals to rate their quality of life on this scale. The MCID is between 0.061 and 0.074 (though this is not specific to obese individuals, see Zhang et al., 2021).

vi. General Well-Being Schedule (Dupuy, 1977). A psychological scale measuring well-being and level of distress; 18 items cover six dimensions that are summarized in a scale of 0 to 110. Scores of 0–60 denote “severe” distress; 61–72 denote “moderate distress”; and 73 to 110 denote “positive well-being.”

HRQoL indicators collected varied on a trial-by-trial basis. Some trials collected multiple indicators, whereas other trials collected on a single indicator.

APPENDIX B: LATENT VARIABLE FOR HRQoL

Health-related quality of life is unobservable. Indicator measures of HRQoL (i.e., SF-36, EQ-5D, etc.) serve, at best, as proxies for the underlying metric of interest. Treated as direct measures of HRQoL, they are vulnerable to measurement error and reporting bias. Many indicators have been applied in studies of BMI: 12 meta-analyses studied in Kolotkin et al. (2017) reported 23 separate measures of HRQoL. Different indicators record and summarize multidimensional HRQoL differently. Thus, establishing which indicator best approximates it (i.e., minimizes measurement error) is not clear. The use of different HRQoL indicators across studies makes comparing HRQoL outcomes problematic. This presents vexing issues in this study where data are jointly modelled. Conventionally, this problem has been approached by mapping between HRQoL indicators (Devlin et al., 2020). This approach is less than ideal because it requires (a) an assumption that the indicator mapped to best approximates HRQoL; (b) that the mapping algorithm used does not induce error; and (c) that algorithms for mapping exist to do so.” Elsewhere, the issue has been addressed by using contingency tables (Warkentin et al., 2014), but here much of the information in the data is lost and only comparable indices (such as generic indicators of HRQoL) are compared. In other meta-analyses, eligibility criteria was the use of the most common HRQoL indicator (SF-36; Ul Haq et al., 2013), which limits the data to analyze because studies that use other indicators are discarded. Here, these issues are avoided by treating HRQoL as a latent variable, treating various HRQoL indicators as such rather than direct measures, and using a system of equations to estimate HRQoL-BMI (see, e.g., Feng et al., 2019, for a similar approach with EQ-5D). This approach relaxes the dependence on the HRQoL indicator to directly measure HRQoL. There is neither a need to assume a best-in-class indicator of HRQoL of those at hand, nor a need to map other HRQoL indicators to it. This approach allows us to dictate the specification of the model and the indicators used. We exploit this to examine BMI variation against both physical and mental HRQoL simultaneously. Further, since we no longer require a single dependent variable for HRQoL, it is possible to use all of the available indicators in the data, that is, multiple indicators for the same individual in a trial.

The latent variable is estimated using information on HRQoL that is contained in the data but not observed, determined in estimation by the fit of the model (under a set of assumptions, e.g., distributional assumptions on error terms). The latent variable uses all of the HRQoL data available. This is shown in Figure B1, where various trials use multiple and different indicators of HRQoL. Models within the system are jointly estimated. There are two types of equation here:

- Measurement equations: which use the indicator of HRQoL, for example, SF-36, as the dependent variable and measure the association of these indicators with the latent variable of HRQoL
- Structural equation: which treats the latent variable of HRQoL as the dependent variable and measures the association between HRQoL and individual characteristics such as BMI.

With these, we measure the relationship between HRQoL and BMI in the structural equation and then how BMI is related to the various indicators of HRQoL through the measurement equations.
Schematic of system of equations for estimating HRQoL as a latent variable and its relationship with BMI. Square boxes are observed data; ellipses are unobserved variables; circles are noise.

**FIGURE B1**

Structural equations:

\[
HRQL_{ijt} = \alpha_i + \gamma_{bmi} BM_{ijt} + \gamma_{bmi_0} BM_{ijt} + \gamma_i Z_{it} + \sum_{j=1}^{4} \gamma_j T_{ijt} + \sum_{t=1}^{4} \delta_t \text{Months since baseline}_{i} + \epsilon_{ijt}
\]

(B1)

Where \(HRQL_{ijt}\) is a latent variable of health-related quality of life. \(\gamma_{bmi}\) is the coefficient of interest, capturing the relationship between BMI and HRQoL. (We then in turn relate changes in BMI to changes in BMI using the \(\gamma\) coefficients in the measurement equations.) \(BM_{ijt}\) are the individual group means of BMI, so as to recover the within estimator from the random effects specification (Bell et al., 2019). \(Z\) is a vector of individual characteristics including age, gender and ethnicity; \(\gamma\) are to be estimated. Trial are trial-specific fixed effects; four parameters, \(\gamma_j\), are estimated for 5 trials as one is set to zero to avoid linear dependency. Months since baseline are time periods (measured in months) since baseline; four parameters, \(\delta_t\), are estimated for 5 time periods as one is set to zero to avoid linear dependency. \(\alpha_i\) is an individual-specific random effect, assumed to be iid normally distributed, with zero mean and variance, \(\sigma^2_{\alpha}\); that is, \(\alpha_i \sim iid \mathcal{N}(0, \sigma^2_{\alpha})\).

For spline regressions, BMI is partitioned into regions of its range, denoted \(BM_{ijt}\) according to the standard BMI classification, omitting underweight as no participants in the study were underweight. \(c = \text{normal weight, overweight, obese category I, obese category II, obese category III.}\) Boundary knots were placed at BMI=18.5 (as per the BMI categorization) and at BMI=55 (due to sparsity of data beyond BMI=55). Parameters for each region, \(\gamma_{bmi,c}\), are estimated. Similarly, the group means are specified for each individual and by grouping.

Next, model (1) was re-specified to consider the relation of longitudinal changes in BMI and HRQoL. The period-to-period BMI changes are used in the linear model. We refer to this model as the delta model to refer to the change in BMI.

\[
HRQL_{ijt} = \alpha_i + \sum_{c=1}^{5} \gamma_{bmi,c} BM_{ijt} + \sum_{c=1}^{5} \gamma_{bmi_0,c} BM_{ijt} + \gamma_i Z_{it} + \sum_{j=1}^{4} \gamma_j T_{ijt} + \sum_{t=1}^{4} \delta_t \text{Months since baseline}_{i} + \epsilon_{ijt}
\]

(B2)

Where \(BM_{ijt}\) = \(BM_{ijt} - BM_{ijt-1}\).

Finally, the longitudinal analogue of model (2) is specified. The period-to-period BMI changes are used in the spline regression. This is termed delta spline regression,

\[
HRQL_{ijt} = \alpha_i + \sum_{c=1}^{5} \gamma_{bmi,c} \Delta BM_{ijt} + \gamma_i Z_{it} + \sum_{j=1}^{4} \gamma_j T_{ijt} + \sum_{t=1}^{4} \delta_t \text{Months since baseline}_{i} + \epsilon_{ijt}
\]

(B3)

Where \(\Delta BM_{ijt}\) = \(BM_{ijt} - BM_{ijt-1}\).

In all specifications, models are fully specified with all possible variables. Models are then iteratively refined by removing non-significant variables, or setting parameters to zero that do not influence the log-likelihood in pre-testing. Models are estimated using simulated log-likelihood (see e.g. Train, 2009). Modified Latin...
Hypercube Sampling (MLHS) draws from a normal distribution are taken to construct the latent variable. Apollo software for R is used for estimation.

Measurement equations:

\[
SF - 36(pcs)_{ijt} = \zeta_{pcs}HRQOL_{ijt} + \epsilon_{ijt,pcs} \tag{B5}
\]

\[
SF - 36(mcs)_{ijt} = \zeta_{mcs}HRQOL_{ijt} + \epsilon_{ijt,mcs} \tag{B6}
\]

\[
FT\ score_{ijt} = \zeta_{ft\ score}HRQOL_{ijt} + \epsilon_{ijt,ft\ score} \tag{B7}
\]

\[
IWQOL_{ijt} = \zeta_{iwqol}HRQOL_{ijt} + \epsilon_{ijt,iwqol} \tag{B8}
\]

\[
EQ - 5D_{ijt} = \zeta_{eq-5d}HRQOL_{ijt} + \epsilon_{ijt,eq5d} \tag{B9}
\]

\[
EIQVAS_{ijt} = \zeta_{eqvase}HRQOL_{ijt} + \epsilon_{ijt,eqvase} \tag{B10}
\]

\[
totwel_{ijt} = \zeta_{totwel}HRQOL_{ijt} + \epsilon_{ijt,totwel} \tag{B11}
\]

where indicators of HRQoL, for example, \(SF - 36(pcs)\), are treated as dependent variables to be explained by the latent variable of HRQoL. Then, the \(\zeta\) capture the association between the indicators of HRQoL and the latent variable for HRQoL.

APPENDIX C: ASSOCIATIONS OF HRQoL AND DEMOGRAPHIC VARIABLES

Females had lower HRQoL than males (estimate = −0.18; 95% CI: −0.35 to −0.01); and black individuals had higher HRQoL than white individuals (estimate = 0.43; 95% CI: 0.23 to 0.64). HRQoL was negatively associated with age. Relative to under-65s, those between ages 65 and 70 had lower HRQoL (estimate = −0.17; 95% CI: −0.24 to −0.09); and those over 70 had lower HRQoL (estimate = −0.66; 95% CI: −0.78 to −0.55). HRQoL was lower in WRAP than LookAHEAD in the spline regression (estimate = −1.01; 95% CI: −1.40 to −0.62) and higher in TOHP than LookAHEAD (estimate = 0.87; 95% CI: 0.71 to 1.03) (Table C1).

### TABLE C1 Associations of covariates and HRQoL

|                      | Linear model |                  |                  | Spline regression |                  |                  |
|----------------------|--------------|------------------|------------------|-------------------|------------------|------------------|
|                      | Est          | 95% CI           | p value          | Est               | 95% CI           | p value          |
| Gamma Female         | −0.18286     | (−0.351 to 0.014)| <0.01            | −0.55191          | (−0.943 to 0.16) | <0.01            |
| Gamma Age category2  | −0.16658     | (−0.238 to 0.094)| <0.01            | −0.28104          | (−0.45 to 0.111) | <0.01            |
| Gamma Age category3  | −0.66396     | (−0.78 to 0.547) | <0.01            | −1.13937          | (−1.621 to 0.656)| <0.01            |
| Gamma Black          | 0.4338       | (0.226 to 0.641) | <0.01            | 0.68008           | (0.164 to 1.195) | <0.01            |
| Gamma Other          | −0.04807     | (−0.335 to 0.239)|                 | 0.0451            | (−0.486 to 0.576)|                 |

Abbreviations: DPP, Diabetes Prevention Programme; Est, estimate; HRQoL, health-related quality of life; TOHP, Trials of Hypertension Prevention; 95% CI, 95% confidence interval.

Note: In the linear model, an additional specification interacts the time-from-baseline variables with trials’ interventions.
APPENDIX D: TIME-FROM-BASELINE CHANGE IN HRQoL

Time-from-baseline fixed effects indicate how HRQoL varied over time for all participants across all of the trials. We estimated this specification for the linear and the spline regressions. In both cases, HRQoL increased from baseline to 12 months and declined thereafter. By 48 months, the level of HRQoL had returned to that at baseline (Table D1 and Figure D1).

|                  | Linear model                      | Spline regression                  |
|------------------|-----------------------------------|------------------------------------|
|                  | Est  | 95% CI          |  p value | Est  | 95% CI          |  p value |
| 12 months        | 0.41 | (0.348 to 0.473) |  <0.01   | 0.86 | (0.514 to 1.198) |  <0.01   |
| 24 months        | 0.20 | (0.141 to 0.251) |  <0.01   | 0.40 | (0.219 to 0.582) |  <0.01   |
| 36 months        | 0.11 | (0.059 to 0.166) |  <0.01   | 0.22 | (0.087 to 0.343) |  <0.01   |
| 48 months        | −0.02| (−0.069 to 0.029) |  0.48    | −0.05| (−0.142 to 0.048) |  0.33    |

Abbreviations: Est, estimate; HRQoL, health-related quality of life; 95% CI, 95% confidence interval.
Note: In the linear model, an additional specification interacts the time-from-baseline variables with trials’ interventions.

FIGURE D1  HRQoL and BMI change over time. Top panel: HRQoL at months after baseline. Lower panel: Period-to-period change in BMI
APPENDIX E: MISSING DATA AND MODELS WITH MULTIPLE IMPUTATION

Look AHEAD

| Variable     | Missing | Total | Percent missing |
|--------------|---------|-------|-----------------|
| pcs          | 16,420  | 78,496| 20.92           |
| mcs          | 16,420  | 78,496| 20.92           |
| bmi          | 33,386  | 78,496| 42.53           |
| age_category | 0       | 78,496| 0.00            |
| t            | 0       | 78,496| 0.00            |
| randarm      | 0       | 78,496| 0.00            |
| female       | 0       | 78,496| 0.00            |
| black        | 0       | 78,496| 0.00            |
| other        | 0       | 78,496| 0.00            |
| heduc        | 0       | 78,496| 0.00            |
| educ_missing | 0       | 78,496| 0.00            |
| unemployed   | 0       | 78,496| 0.00            |
| unemployed~g | 0       | 78,496| 0.00            |
| current_sm~r | 0       | 78,496| 0.00            |
| past_smoker  | 0       | 78,496| 0.00            |
| cvdhistory   | 0       | 78,496| 0.00            |
| use_of_ins~n | 0       | 78,496| 0.00            |
| hypertension | 0       | 78,496| 0.00            |

DPP

| Variable     | Missing | Total | Percent missing |
|--------------|---------|-------|-----------------|
| sfqal        | 8880    | 15,405| 57.64           |
| bmi          | 8204    | 15,405| 53.26           |
| female       | 0       | 15,405| 0.00            |
| black        | 0       | 15,405| 0.00            |
| hispanic     | 0       | 15,405| 0.00            |
| other        | 0       | 15,405| 0.00            |
| years_diab~s | 0       | 15,405| 0.00            |
| heart_dise~e | 0       | 15,405| 0.00            |
| stroke_bas~e | 0       | 15,405| 0.00            |
| hours_sleep  | 4116    | 15,405| 26.72           |
| total_work   | 6322    | 15,405| 41.04           |
| total_hous~k | 4312    | 15,405| 27.99           |
| total_recr~n | 4163    | 15,405| 27.02           |
| alcohol_pe~k | 6903    | 15,405| 44.81           |
| past_30_da~g | 6903    | 15,405| 44.81           |

WRAP

| Variable     | Missing | Total | Percent missing |
|--------------|---------|-------|-----------------|
| eq5d         | 1448    | 5068  | 28.57           |
| eq_vas       | 1398    | 5068  | 27.58           |
| bmi~         | 1118    | 5068  | 22.06           |
| female       | 0       | 5068  | 0.00            |
| nonwhite     | 0       | 5068  | 0.00            |
| age_category | 0       | 5068  | 6.08            |
| levelofedu~0 | 308     | 5068  | 6.08            |
| household~e_ | 2056    | 5068  | 40.57           |
| household~s_ | 2102    | 5068  | 41.48           |
| bloodpress~_ | 2499    | 5068  | 49.31           |
| lipidlower~_ | 2499    | 5068  | 49.31           |
| diabetesmed_ | 2499    | 5068  | 49.31           |
| obesitymed_  | 2499    | 5068  | 49.31           |
| antidepres~_ | 2499    | 5068  | 49.31           |

TOHP

| Variable     | Missing | Total | Percent missing |
|--------------|---------|-------|-----------------|
| totwel       | 1676    | 6546  | 25.60           |
| bmi          | 1621    | 6546  | 24.76           |
| female       | 0       | 6546  | 0.00            |
| black        | 0       | 6546  | 0.00            |
| other        | 0       | 6546  | 0.00            |
| college      | 0       | 6546  | 0.00            |
| employed     | 0       | 6546  | 0.00            |
| age          | 0       | 6546  | 0.00            |

DioGENES

| Variable     | Missing | Total | Percent missing |
|--------------|---------|-------|-----------------|
| iwqoltot_    | 1320    | 3363  | 39.25           |
| bmi          | 1087    | 3363  | 32.32           |
| female       | 0       | 3363  | 0.00            |
| black        | 0       | 3363  | 0.00            |
| other        | 0       | 3363  | 0.00            |
| married      | 0       | 3363  | 0.00            |
| age          | 543     | 3363  | 16.15           |

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Table E1 is as follows.

**TABLE E1** Comparison of non-imputed and imputed estimates for each of five trials

|                | DioGENES | DPP | Look AHEAD |
|----------------|----------|-----|------------|
|                | OLS      | FE  | Spline     | OLS      | FE  | Spline     | OLS      | FE  | Spline     |
|                | raw      | MI  | raw        | MI        | Raw | MI         | raw      | MI  | Raw        | MI         | Raw   | MI         |
| BMI            | -0.724 (-3.85) | 0.721 (-4.76) | -0.739 (-2.26) | -0.799 (-3.39) | 0.000 (0.49) | 0.000 (-0.06) | 0.002 (1.11) | 0.000 (-0.06) | -0.435 (-25.79) | -0.432 (-37.92) | -0.506 (-24.69) | -0.318 (-33.12) |
| BM1            |          |     |            |           |     |            |           |     |            |           |      |            |           |
| BM11           | 0 ()     | 0 () |            |           |     |            |           |     |            |           |      |            |           |
| BM2            | 1.096 (0.23) | 1.323 (-0.27) |            |           |     |            |           |     |            |           |      |            |           |
| BM3            | -1.578 (-2.19) | -1.627 (-2.31) |            |           |     |            |           |     |            |           |      |            |           |
| BM4            | 0.372 (0.85) | 0.361 (-0.8)  |            |           |     |            |           |     |            |           |      |            |           |
| BM5            | -1.862 (-3.90) | -1.794 (-3.67) |            |           |     |            |           |     |            |           |      |            |           |
| BM6            | 0 ()     | 0 () |            |           |     |            |           |     |            |           |      |            |           |

Note: Three models are compared for each trial: OLS, fixed effects (FE) and spline regressions (spline). For each model, parameter estimates from the model on the raw data (raw) are presented next to those on the imputed data (MI) with robust t-ratios in parentheses.

**TABLE E1** Continued

|                | TOHP     | WRAP |
|----------------|----------|------|
|                | OLS      | FE   | OLS      | FE   |
|                | raw      | MI   | raw      | MI   |
| BMI            | -0.281 (-4.28) | -0.283 (-4.81) | -0.683 (-5.03) | -0.303 (-4.80) | -0.009 (-6.69) | -0.010 (-8.55) | -0.008 (-3.96) | -0.009 (-4.58) |
| BM1            | 0 ()     | 0 () |            |           |     |            |           |     |            |           |      |            |           |
| BM2            | 0.119 (0.39) | 0.153 (-0.64) |            |           |     |            |           |     |            |           |      |            |           |
| BM3            | -0.3 (-3.54) | -0.308 (-5.06) |            |           |     |            |           |     |            |           |      |            |           |
| BM4            | -0.322 (-5.26) | -0.308 (-6.74) |            |           |     |            |           |     |            |           |      |            |           |
| BM5            | -0.899 (-14.55) | -0.902 (-21.46) |            |           |     |            |           |     |            |           |      |            |           |
| BM6            | 0 ()     | 0 () |            |           |     |            |           |     |            |           |      |            |           |

Note: Three models are compared for each trial: OLS, fixed effects (FE) and spline regressions (spline). For each model, parameter estimates from the model on the raw data (raw) are presented next to those on the imputed data (MI) with robust t-ratios in parentheses.
APPENDIX F: DIAGNOSTIC INFORMATION FROM THE ESTIMATED MODELS

Table F1 is as follows.

**TABLE F1** Model diagnostics

|                       | Cross section |          | Delta |          |
|-----------------------|---------------|----------|-------|----------|
|                       |               | Linear   | Spline| Linear   | Spline  |
| No. of individuals    | 10,884        | 10,884   | 8531  | 8531     |
| No. of observations   | 58,719        | 58,719   | 27,715| 27,715   |
| Estimated parameters  | 29            | 33       | 23    | 26       |
| Simulated log-likelihood (full fitted model) | –509,624.7 | –509,944.4 | –238,724.3 | –238,722.4 |
| AIC (full fitted model) | 1,019,307     | 1,019,955 | 477,494.6 | 477,496.8 |
| BIC (full fitted model) | 1,019,595     | 1,020,282 | 477,705 | 477,734.6 |
| Simulated log-likelihood (measurement equation: pcs) | –149,861 | –149,997.1 | –71,881.56 | –71,870.63 |
| Simulated log-likelihood (measurement equation: mcs) | –155,600.1 | –155,668 | –74,093.12 | –74,093.65 |
| Simulated log-likelihood (measurement equation: ft) | –172,332 | –172,623.6 | –82,508.44 | –82,508.82 |
| Simulated log-likelihood (measurement equation: iwqol) | –172,332 | –8684.095 | –2147.588 | –2147.694 |
| Simulated log-likelihood (measurement equation: eqvas) | 2114.198 | 2104.347 | 719.3283 | 716.1988 |
| Simulated log-likelihood (measurement equation: eq5d) | 2114.198 | 647.1308 | 301.0425 | 300.6449 |
| Simulated log-likelihood (measurement equation: well) | –18,063.81 | –18,039.41 | –9696.251 | –9698.8 |

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; NB, different numbers of draws were required for the models to facilitate estimation, thus direct comparison of the simulated log-likelihood is not appropriate.

Note: Simulated log-likelihoods for the full model and for the measurement equations are presented—one for each of the HRQoL indicators.

APPENDIX G: SENSITIVITY ANALYSIS USING ONLY PARTICIPANTS IN THE CONTROL ARMS OF THE TRIALS

Table G1 is as follows.

**TABLE G1** Estimated BMI coefficient and diagnostics from model using only individuals in the control arms of trials

|                              | Estimate | 95% CI           | p value |
|------------------------------|----------|------------------|---------|
| BMI                          | –0.122   | (–0.134 to –0.110) | <0.01   |
| No. of Individuals           | 4258     |                  |         |
| No. of Observations          | 26,556   |                  |         |
| Estimated parameters         | 29       |                  |         |
| Simulated log-likelihood (full fitted model) | –248,039.2 |                  |         |
| AIC (full fitted model)      | 496,136.4 |                  |         |
| BIC (full fitted model)      | 496,401.6 |                  |         |

Abbreviations: AIC, Akaike information criteria; BIC, Bayesian information criteria; Est, estimate; 95% CI, 95% confidence interval.
APPENDIX H: BASELINE AVERAGE HRQoL VALUES AT BMI CATEGORIES

Table H1 as follows.

| BMI category: | SF-36 pcs | SF-36 mcs | IWQoL | Feelings thermometer | EQ-5D | EQ VAS | Well-being |
|---------------|-----------|-----------|-------|----------------------|-------|--------|------------|
| Underweight   | 74.5      |           |       |                      |       |        |            |
| Normal Weight | 50.5      | 51.2      | 67.7  | 85.0                 |       | 76.3   | 81.6       |
| Overweight    | 50.4      | 54.1      | 66.0  | 77.9                 | 0.8   | 72.6   | 78.8       |
| Obese Class I | 49.4      | 54.3      | 64.2  | 75.9                 | 0.8   | 65.9   | 78.5       |
| Obese Class II| 47.6      | 53.8      | 59.7  | 73.3                 | 0.8   |        |            |
| Obese Class III| 44.8     | 54.4      | 54.2  | 70.0                 | 0.7   | 63.8   |            |

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