Appendix 1: Effect of loneliness on health outcomes

Table 2. The magnitude of the effect of loneliness on adverse health outcomes

Health outcome	Loneliness	Social isolation	Evidence type	Main source
Mortality	OR: 1.26 (95% CI 1.04 to 1.53)	OR: 1.29 (95% CI 1.06 to 1.56).	Meta analysis	Holt-Lunstad et al. (2015)
Cardiovascular disease	RR: 1.29 (95% CI 1.04 to 1.59) HR: 1.16 (95% CI, 1.10 to 1.22)[1]		Meta analysis	Valtorta et al. (2016) Albasheer et al. (2024)
Stroke	RR: 1.32, (95% CI 1.04 to 1.68)[1]		Meta analysis	Valtorta et al. (2016)
Dementia and Alzheimer's Disease	RR: 1.26 (95% CI 1.14 to 1.40)	RR: 0.88 (95% CI 0.80 to 0.96)	Meta analysis	Lara et al. (2019) Penninkilampi et al. (2018)
Blood pressure	OR: 1.31 (95% CI 1.04 to 1.66)		Single study	Momtaz et al.,(2012)
Depression	OR: 2.33 (95% CI 1.62 to 3.34)		Meta analysis	Mann et al. (2022)

[1] These studies are on the impact of "social relationships" and not loneliness

Suicidal ideation/ behaviour	r = .21 (95% CI .14 to .28)		Meta analysis	McClelland et al. (2020)
Anxiety	r = .417 (95% CI .469 to .312)		Meta analysis	Park et al. (2020)
Sleep disturbance	r = .28 (95% CI .24 to .33) OR: 1.75 (95% CI 1.511 to 2.026)		Meta analysis	Griffin et al. (2020) Deng et al. (2023)
Primary health care usage	r = .094 (95% CI .07 to .12)		Meta analysis	Sirois and Owens, (2023)
Self-rated general Health	r = .358, (95% CI .470, .286)		Meta analysis	Park et al. (2020)
Diabetes	HR: 1.46, (95% CI 1.15 to 1.84)		Single studies	Hackett et al., (2020)

Appendix 2: Methods

Observational analysis

We employed multivariate regression analysis using data from participants in UK Biobank to conduct our observational analysis. This method allows us to see how different factors are related to each other while controlling for the effect of other factors.

We ran our analysis in three different ways to control for various factors that might influence the results:

1. Controlling for no other factors: we looked at the relationship between loneliness, social isolation, and health without controlling for any other factors that might influence the results;
2. Controlling for demographic and socio-economic factors: The factors included were age, sex, the location where participants were assessed in the UK Biobank study, a measure of deprivation in their area, years of education, household income, and ethnicity;
3. Controlling for demographic and socio-economic factors, disability and adverse childhood experiences: We control for disability and adverse childhood experiences in addition to everything else controlled for in 2.

By running the analysis in these three ways, we were able to get a clearer picture of how loneliness and social isolation are related to health outcomes while considering how other factors might play a role in this relationship. Note that in the results section, we only present the results for the third analysis, where we control for the most factors.

Strengths and weaknesses of observational analysis

Strengths	Weaknesses
Large sample size.	Cannot fully determine if relationships are causal because of confounding factors and potential reverse causality.
Able to control for a range of factors.	There are many factors we can't or don't control for which can bias results.

Sibling control analysis

For this part of the study, we only used data from siblings who participated in the UK Biobank (i.e., 2 or more siblings in a family with data). We used a similar approach as for our observational analysis, running multivariate regression analysis in three different ways to control for other factors that might affect the results. Note again that in the results section, we only present the results for the third analysis, where we control for the most factors.

In these analyses, we get two types of effects:

- The between-family effect: This is the average effect of siblings' loneliness and social isolation on their health outcomes. It tells us how the relationship looks across different families.
- The within-family effect: This is each sibling's deviation from the average sibling effect. It tells us how the relationship looks within the same family, comparing one sibling to another.

Of the two, the "within-family effect" is the effect that we expect to be closer to the true causal effect of loneliness and social isolation on health outcomes. This is because the within-family effect controls the many things siblings share in common, such as their genes and the environment they were raised in. This is the effect we report in the main text.

What advantage does this have over observational analysis?

In a regular observational study, we can only control for factors that we can measure and have in our data, such as age, income, or education level. However,

there are many other factors that can influence both loneliness and health that we might not be able to measure or have in our data.

When we study siblings and look at our "within-family effect", we can control for some of these unmeasured factors because siblings share many of the same genes and often grow up in the same environment. By comparing siblings to each other, we can effectively cancel out the impact of these shared factors, even if we can't directly measure them.

Strengths and weaknesses of sibling control analysis (for the within-family effect)

Strengths	**Weaknesses**
Able to control for some shared environmental and genetic unmeasured confounding.	Other unmeasured confounding still may be problematic.
	Sample size is smaller as only siblings are included in analyses.
	Results may be less generalisable because individuals with siblings may not be representative of the average loneliness and social isolation experience.

Mendelian randomisation

Mendelian randomisation analyses allow us to get a better picture of whether one factor causally influences another. This is because it draws on the fact that our genes are randomly assigned to us from both of our parents at conception and that they cannot be changed once assigned. Mendelian randomisation uses the fact that genes that increase the likelihood of experiencing loneliness and social isolation are randomly assigned to examine whether people genetically predisposed to loneliness and social isolation are more likely to experience particular health outcomes.

In our study, we used two types of Mendelian randomisation analysis:

- One-sample Mendelian randomisation: Information on genes related to loneliness and social isolation and these measured factors are obtained from the same sample of individuals;
- Two-sample Mendelian randomisation: In this approach, we also use information on genes that may increase the likelihood of a given health outcome (a different set of genes to those related to loneliness and social isolation). Information on genes related to loneliness and social isolation comes from one sample of individuals. Information on genes related to each of our health outcomes comes from a second sample of individuals.

Here we only report the results from one of these analyses. If available, we report the two-sample result as our Mendelian Randomisation result. If not, we report the one-sample result. Complete results are available in the technical report.

We also conducted a number of additional sensitivity analyses which are detailed in the technical report. Some of these were included to determine whether the genetic variants related to loneliness or social isolation only affect the health outcome via its effects on loneliness or social isolation (a key assumption of Mendelian randomisation). Others were included to examine relationships under other assumptions or potential weaknesses. A short video summarising Mendelian randomisation can be viewed here.

What advantage does this have over observational analysis?

In observational analysis, we look at how different factors are related to each other whilst controlling for the effect of other factors. However, there are still other factors we cannot measure or control for. In Mendelian randomisation, we can control for these unmeasured factors to a greater degree and get a better idea of the causal effect. By doing this we can have a better understanding of whether one factor may cause another.

Strengths and weaknesses of Mendelian randomisation

Strengths	**Weaknesses**
Less prone to confounding factors.	Loneliness and social isolation are likely to be related to the genetic variants used here through complex and indirect pathways. Mendelian randomisation is considered more reliable when there are more direct pathways from genetic variants to traits.
Less prone to issues around reverse causation.	Sensitivity analyses are a useful tool but they cannot rule out the possibility that the genes identified by the method affect health outcomes through pathways other than loneliness or social isolation.
A range of sensitivity analyses can be used to test the assumptions of the approach.	Effect estimates are difficult to meaningfully interpret.

Appendix 3: Measures

Table 3: Loneliness, social isolation and health measures

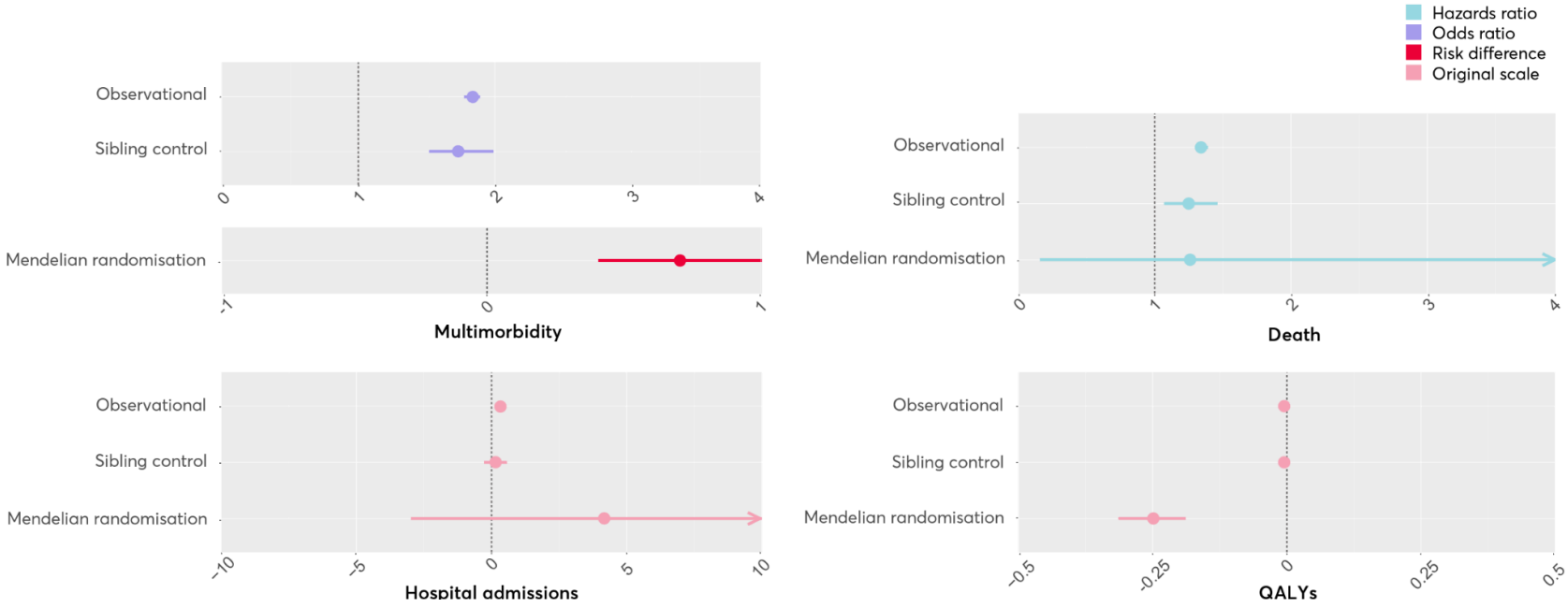
	UK Biobank measures	**Measures used in the datasets for associations with genetic variants**
Methods using this data	Observational, sibling control and Mendelian randomisation	Mendelian randomisation
Exposures		
Loneliness	Asked whether they often felt lonely. A binary measure.	Combination of questions asking whether they felt lonely and questionnaires around loneliness
Social isolation	Combined measure from questions on how often they see friends/family and how many people are living in their household. On a scale of 0 to 2.	Combined measure from questions around how often they see friends/family and how many people are living in their household
General health		
Quality-adjusted life years (QALYs)	A measure that reflects the quantity and quality of life and which was measured from health conditions reported in hospital electronic healthcare records. A value of 1 indicates a full year of perfect health for a full year.	-

Death	Whether death occurred in the follow-up period	-
Hospital admissions	The number of hospital admissions	-
Multimorbidity (having multiple health conditions)	The presence of two or more self-reported chronic conditions	-
Physical health		
Coronary artery disease (CAD)	Whether the person was diagnosed with CAD in the follow-up period	A combination of diagnosis information from several sources
Systolic blood pressure (SBP)	Systolic blood pressure - an average of two readings. Systolic blood pressure is the pressure against arteries when the heart is pumping blood.	Systolic blood pressure readings obtained in different settings
Heart failure	Whether the person was diagnosed with heart failure in the follow-up period	A combination of diagnosis information from several sources
Stroke	Whether the person was diagnosed with stroke in the follow-up period	A combination of diagnosis information from several sources
Type 2 diabetes (T2D)	An algorithm was used to determine if someone had 'possible' or 'probable' type 2 diabetes based on a range of measures	A combination of diagnosis information from several sources

Mental health and wellbeing		
Self-harm	Asked whether they had deliberately harmed themselves	-
Suicide attempt	Asked whether they had harmed themselves with the intention to end their life	Obtained yes/no responses from a variety of sources
Depression diagnosis	Diagnosis of depression from self-report	A combination of diagnosis information from several sources
Depression trait	A score from the PHQ-9 questionnaire	-
Anxiety	Diagnosis of anxiety from self-report	A combination of diagnosis information from several sources
Anxiety trait	A score from the GAD-7 questionnaire	-
Wellbeing spectrum	-	A spectrum including life satisfaction, positive affect, neuroticism and depressive symptoms
Positive affect	Asked how happy they are	Combination of measures around feeling happy and positive emotions
Life satisfaction	-	Combination of measures around the longer-term evaluation of their life
Meaning in life	Asked to what extent they feel their life to be meaningful	-

Appendix 4: Results figures and tables

Figure 1. Results for loneliness and general health outcomes



Notes: The points represent the estimated effects, with the horizontal lines indicating the 95% confidence intervals around these estimates. The dotted vertical lines mark the null line, representing the point at which there is no association observed.

Table 4. Results for loneliness and general health outcomes

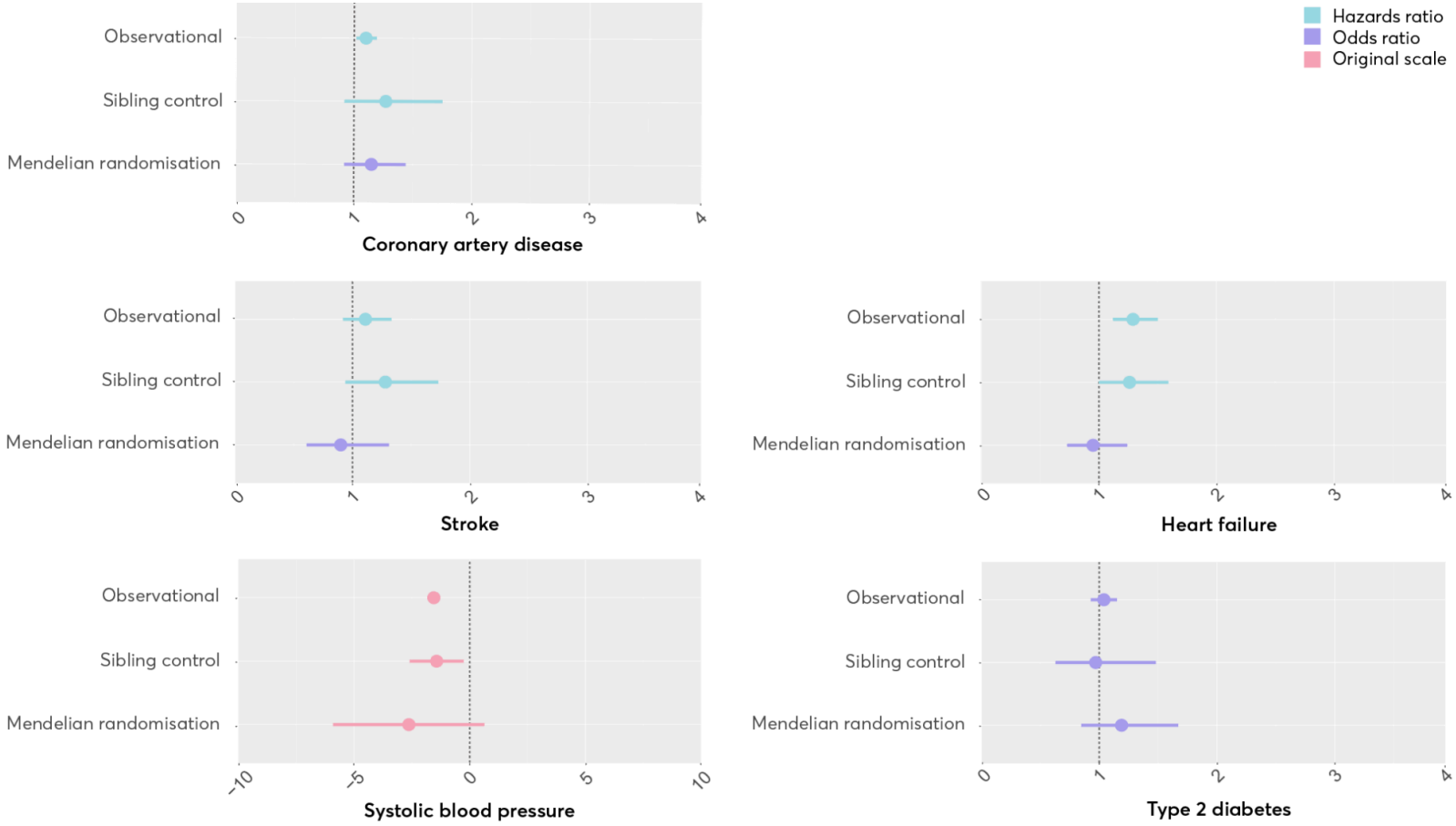
Outcome	Observational		Sibling control		Mendelian Randomisation	
	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a,b]
Death	332,507	HR: 1.34 (95% CI: 1.30 to 1.39; p<0.001)	32,828	HR: 1.25 (95% CI: 1.07 to 1.46; p=0.006)	331,995	HR: 1.26 (95% CI: 0.16 to 9.79; p=0.83)
Multimorbidity	118,947	OR: 1.85 (95% CI: 1.78 to 1.91; p<0.001)	12,319	OR: 1.73 (95% CI: 1.49 to 2.02; p<0.001)	331,918	RD: 0.71 (95% CI: 0.41 to 1.01; p<0.001)
Hospital admissions	118,965	0.33 (95% CI: 0.22 to 0.43; p<0.001)	12,322	0.15 (95% CI: -0.27 to 0.57; p=0.50)	331,996	4.17 (95% CI: -2.98 to 11.33; p=0.25)
Quality adjusted life years (QALYs)	93,307	-0.01 (95% CI: -0.02 to -0.01; p<0.001)	9,837	-0.01 (95% CI: -0.02 to -0.001; p=0.03)	269,905	-0.25 (95% CI: -0.38 to -0.13; p<0.001)

HR=hazards ratio, OR=odds ratio, RD=risk difference, CI=confidence intervals

[a]*For continuous outcomes this is an effect estimate on the original scale of the outcome. For Hospital admissions this is a count of times they have been admitted to hospital, for QALYs this is the percentage change in QALYs per year of follow-up.*

[b] *For some binary outcomes this is the approximate risk difference of the outcome per unit increase in genetically predicted loneliness and for continuous outcomes this is the mean difference in the outcome per unit increase in genetically predicted loneliness*

Figure 2. Results for loneliness and physical health outcomes



Notes: The points represent the estimated effects, with the horizontal lines indicating the 95% confidence intervals around these estimates. The dotted vertical lines mark the null line, representing the point at which there is no association observed.

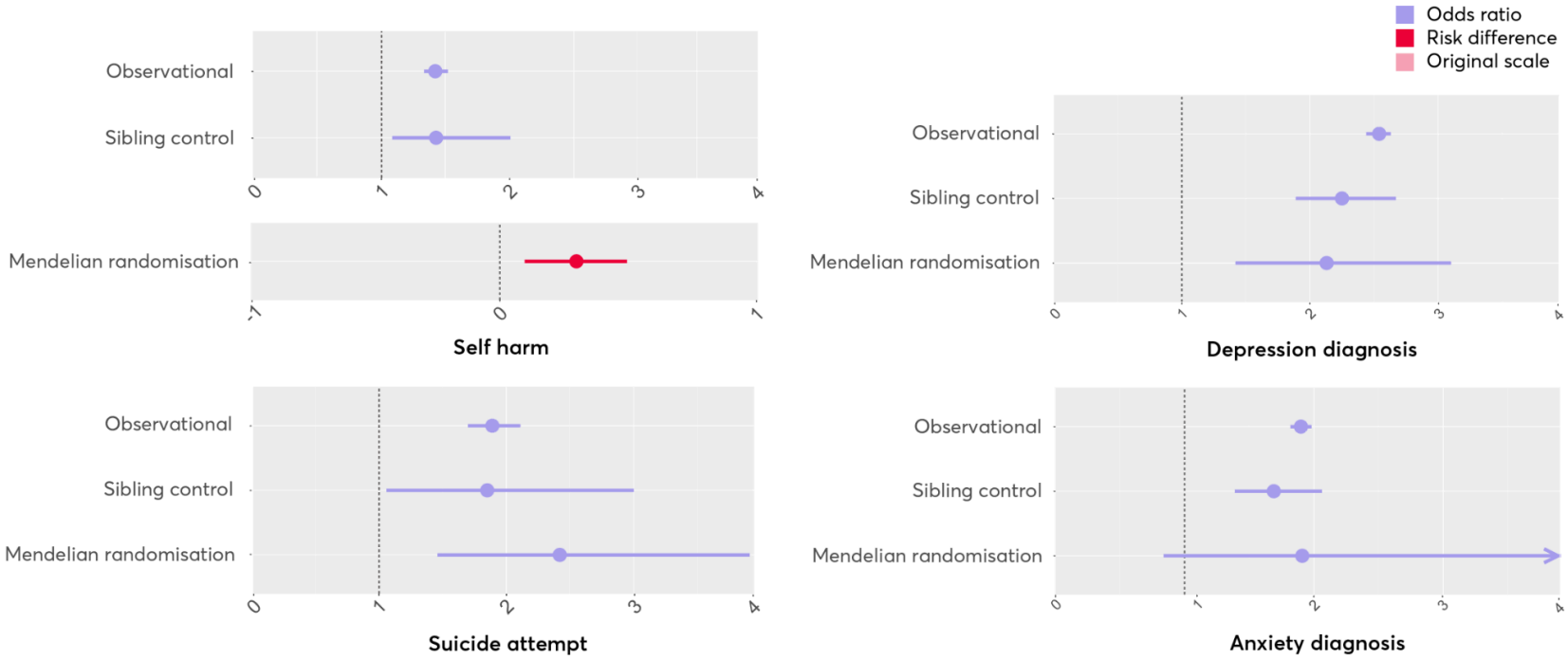
Table 5. Results for loneliness and physical health outcomes

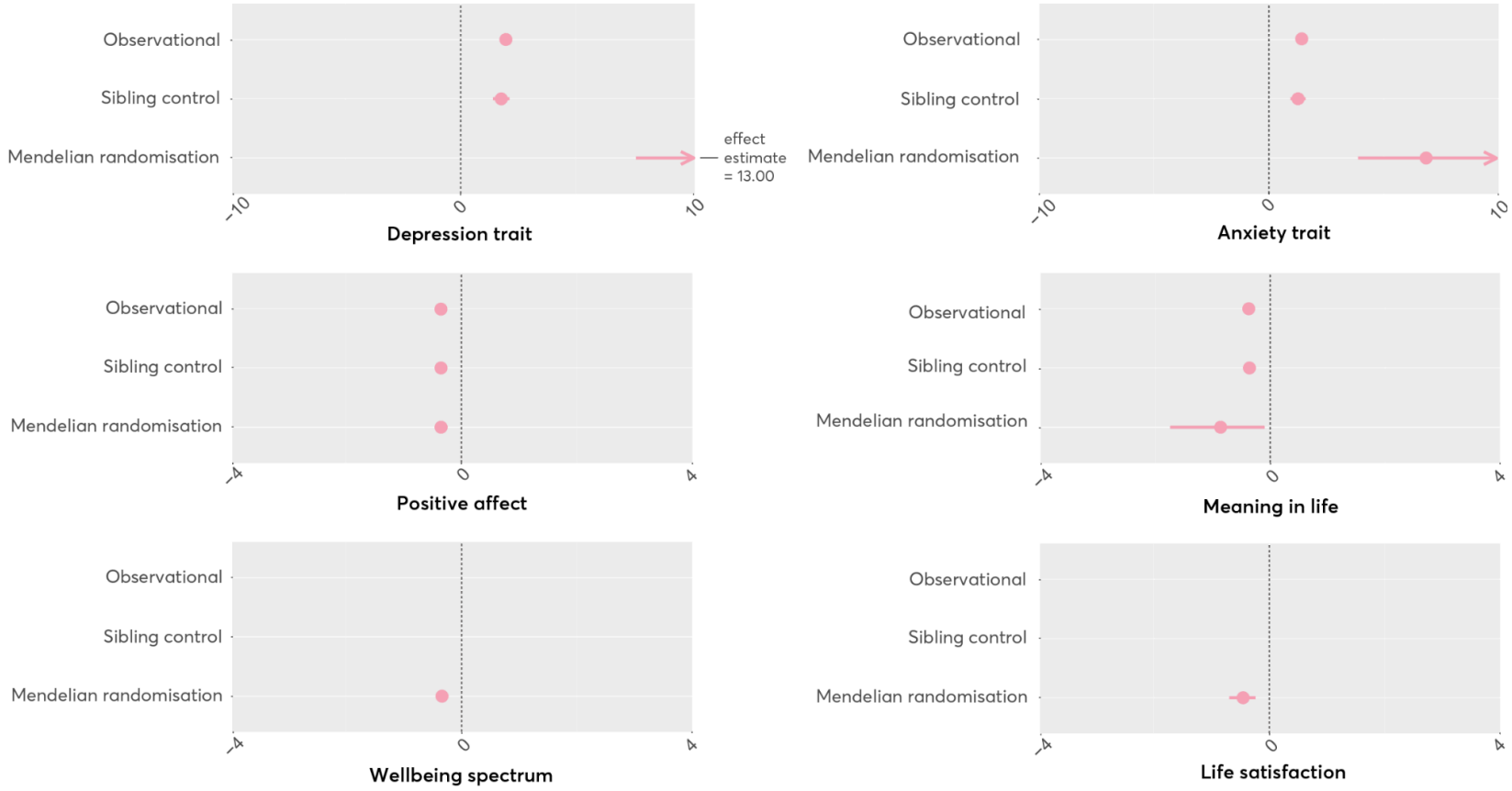
Outcome	Observational		Sibling control		Mendelian randomisation	
	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]
Coronary artery disease	115,557	HR: 1.10 (95% CI: 1.02 to 1.19; p=0.02)	11,959	HR: 1.27 (95% CI: 0.92 to 1.75; p=0.14)	1,347,212	OR: 1.15 (95% CI: 0.92 to 1.44; p=0.22)
Heart failure	118,693	HR: 1.29 (95% CI: 1.12 to 1.50; p<0.001)	32,667	HR: 1.26 (95% CI: 1.00 to 1.59; p=0.05)	977,323	OR: 0.95 (95% CI: 0.73 to 1.24; p=0.72)
Stroke	117,889	HR: 1.11 (95% CI: 0.92 to 1.33; p=0.29)	32,310	HR: 1.28 (95% CI: 0.94 to 1.73; p=0.12)	1,308,460	OR: 0.90 (95% CI: 0.61 to 1.31; p=0.58)
Type 2 diabetes	118,965	OR: 1.04 (95% CI: 0.93 to 1.15; p=0.50)	12,322	OR: 0.97 (95% CI: 0.63 to 1.48; p=0.87)	1,114,458	OR: 1.19 (95% CI: 0.85 to 1.67; p=0.31)
Systolic blood pressure	118,876	-1.55 (95% CI: -1.82 to -1.28; p<0.001)	12,317	-1.43 (95% CI: -2.59 to -0.27; p=0.02)	757,601	-2.63 (95% CI: -5.90 to 0.63; p=0.11)

HR=hazards ratio, OR=odds ratio, CI=confidence intervals,

[a]For continuous outcomes this is an effect estimate on the original scale of the outcome. For systolic blood pressure this is in millimetres of mercury (mmHg).

Figure 3. Results for loneliness and mental health and wellbeing outcomes





Notes: The points represent the estimated effects, with the horizontal lines indicating the 95% confidence intervals around these estimates. The dotted vertical lines mark the null line, representing the point at which there is no association observed.

Table 6. Results for loneliness and mental health and wellbeing outcomes

Outcome	Observational		Sibling control		Mendelian randomisation	
	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a,b]
Self-harm	79,000	OR: 1.86 (95% CI: 1.72 to 2.02; p<0.001)	8,154	OR: 1.69 (95% CI: 1.13 to 2.54; p=0.01)	108,966	RD: 0.31 (95% CI: 0.08 to 0.54; p=0.008)
Suicide attempt	78,904	OR: 1.89 (95% CI: 1.70 to 2.11; p<0.001)	8,146	OR: 1.85 (95% CI: 1.06 to 3.24; p=0.03)	518,612	OR: 2.42 (95% CI: 1.46 to 3.99; p<0.001)
Depression diagnosis	118,965	OR: 2.54 (95% CI: 2.44 to 2.63; p<0.001)	12,322	OR: 2.25 (95% CI: 1.89 to 2.67; p<0.001)	142,646	OR: 2.13 (95% CI: 1.42 to 3.20; p<0.001)
Depression trait	78,213	2.14 (95% CI: 2.05 to 2.22; p<0.001)	8,077	1.77 (95% CI: 1.41 to 2.12; p<0.001)	107,357	13.00 (95% CI: 7.62 to 18.37; p<0.001)
Anxiety diagnosis	118,965	OR: 1.90 (95% CI: 1.82 to 1.98; p<0.001)	12,322	OR: 1.69 (95% CI: 1.39 to 2.06; p<0.001)	17,526	OR: 1.91 (95% CI: 0.84 to 4.36; p=0.12)
Anxiety trait	78,513	1.60 (95% CI: 1.52 to 1.68; p<0.001)	8,100	1.27 (95% CI: 0.94 to 1.59; p<0.001)	107,853	7.81 (95% CI: 3.88 to 11.74; p<0.001)

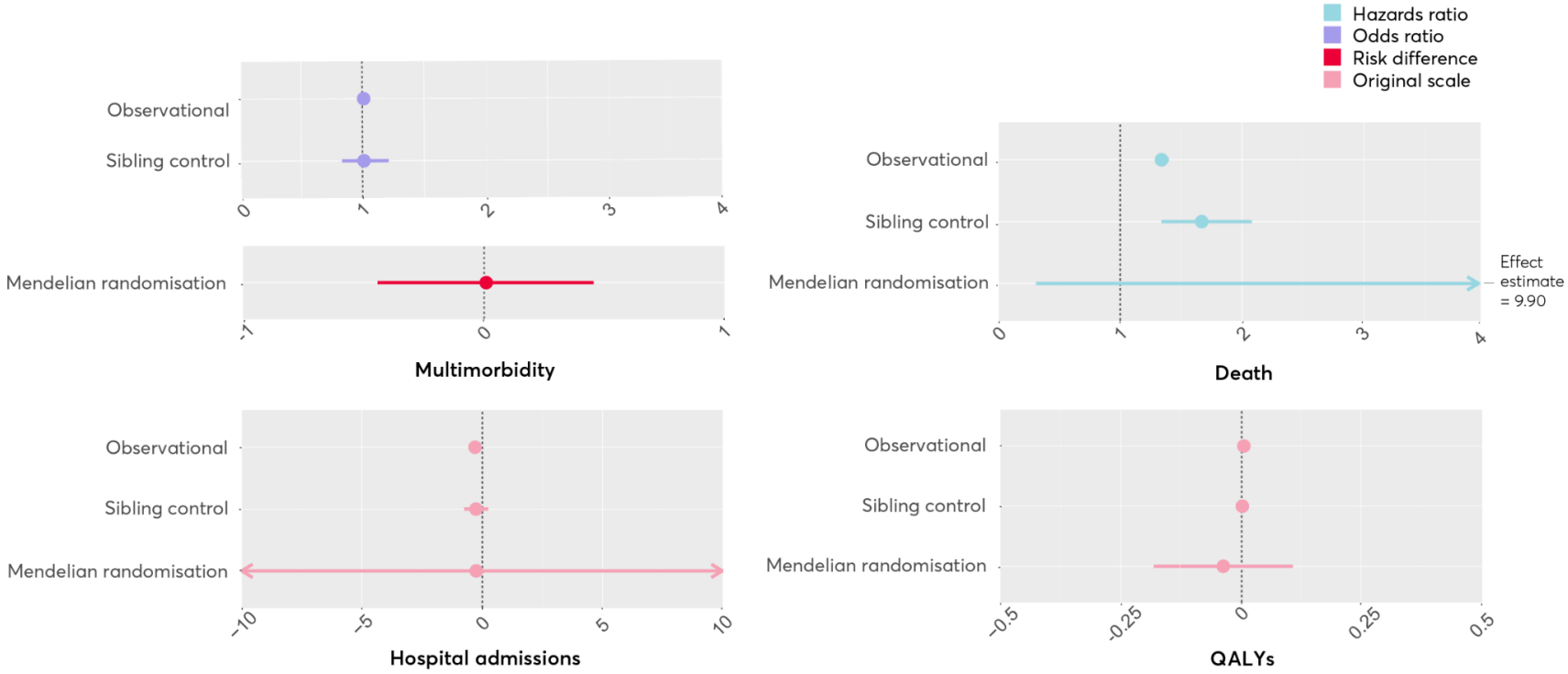
Wellbeing spectrum	-	-	-	-	2,083,151	-0.28 (95% CI: -0.32 to -0.23; p<0.001)
Positive affect/ happiness	92,761	-0.52 (95% CI: -0.53 to -0.51; p<0.001)	9,464	-0.44 (95% CI: -0.50 to -0.39; p<0.001)	410,603	-0.35(95% CI: -0.46 to -0.24; p<0.001)
Life satisfaction	-	-	-	-	523,783	-0.47 (95% CI: -0.69 to -0.24; p<0.001)
Meaning in life	77,577	-0.43 (95% CI: -0.45 to -0.41; p<0.001)	8,004	-0.34 (95% CI: -0.41 to -0.26; p<0.001)	106,828	-0.92 (95% CI: -1.74 to -0.10 p=0.03)

OR=odds ratio, RD=risk difference, CI=confidence intervals

[a]*For continuous outcomes this is an effect estimate on the original scale of the outcome. For the depression trait this is a score ranging from 0 to 27, for the anxiety trait this is a score ranging from 0 to 21, for positive affect in UK Biobank this is a rating ranging from 1 to 6, for meaning in life this is a score ranging from 1 to 5.*

[b] *For some binary outcomes this is the approximate risk difference of the outcome per unit increase in genetically predicted loneliness and for continuous outcomes this is the mean difference in the outcome per unit increase in genetically predicted loneliness*

Figure 4. Results for social isolation and general health outcomes



Notes: The points represent the estimated effects, with the horizontal lines indicating the 95% confidence intervals around these estimates. The dotted vertical lines mark the null line, representing the point at which there is no association observed.

Table 7. Results for social isolation and general health outcomes

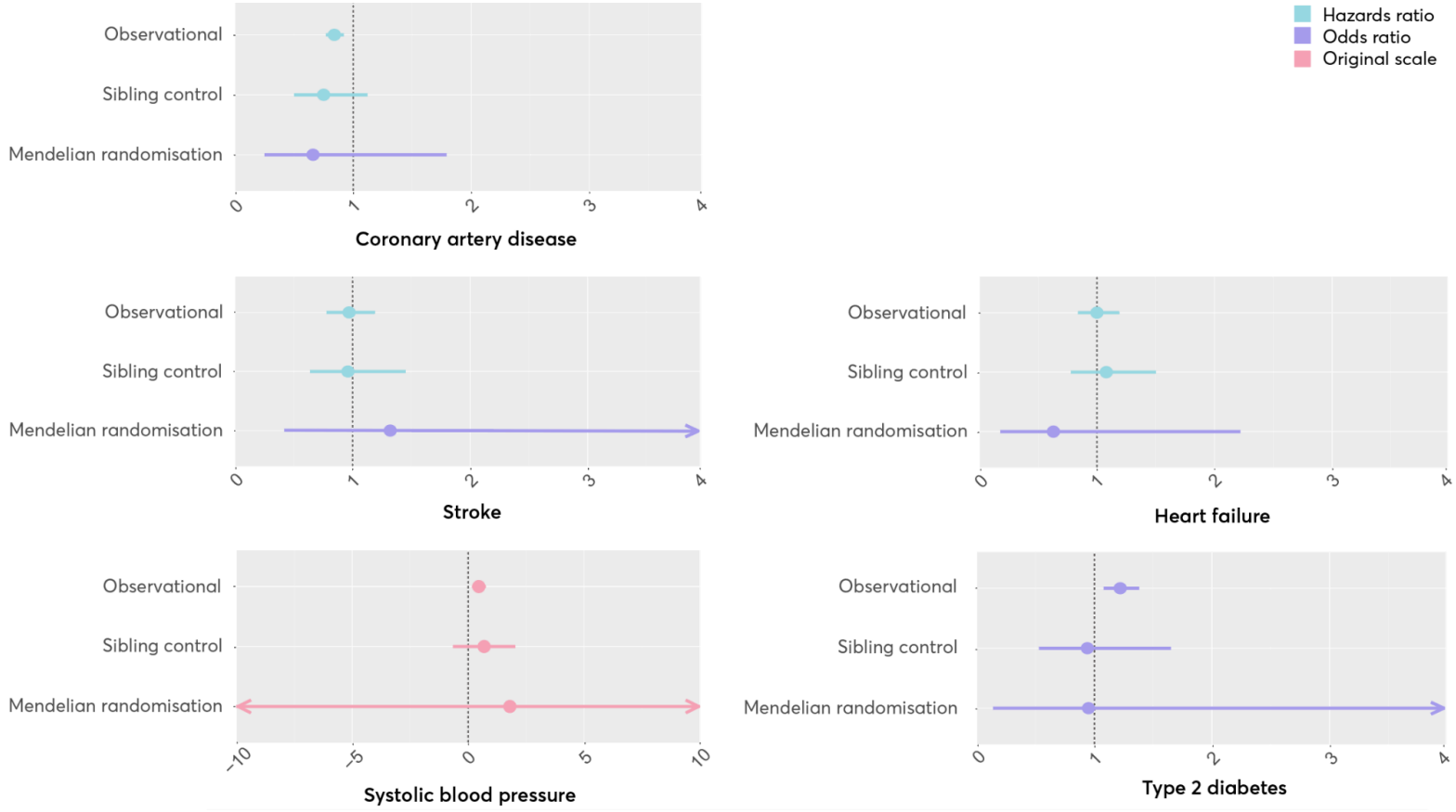
Outcome	Observational		Sibling control		Mendelian randomisation	
	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a,b]
Death	335,593	HR: 1.34 (95% CI: 1.29 to 1.40; p<0.001)	33,325	HR: 1.67 (95% CI: 1.34 to 2.08; p<0.001)	333,357	HR: 9.90 (95% CI: 0.31 to 314.75; p=0.19)
Multimorbidity	119,929	OR: 1.05 (95% CI: 1.01 to 1.09; p=0.02)	12,451	OR: 1.05 (95% CI: 0.88 to 1.25; p=0.61)	333,280	RD: 0.02 (95% CI: -0.41 to 0.45; p=0.92)
Hospital admissions	119,947	-0.30 (95% CI: -0.41 to -0.20; p<0.001)	12,454	-0.26 (95% CI: -0.75 to 0.24; p=0.31)	333,358	-0.25 (95% CI: -12.18 to 11.67; p=0.97)
Quality-adjusted life years (QALYs)	94,086	0.006 (95% CI: 0.004 to 0.009; p<0.001)	9,950	0.002 (95% CI: -0.009 to 0.01; p=0.70)	270,935	-0.05 (95% CI: -0.24 to 0.14; p=0.62)

HR=hazards ratio, OR=odds ratio, RD=risk difference, CI=confidence intervals

[a] *For continuous outcomes this is an effect estimate on the original scale of the outcome. For Hospital admissions this is a count of times they have been admitted to hospital, for QALYs this is the percentage change in QALYs per year of follow-up.*

[b] *For some binary outcomes this is the approximate risk difference of the outcome per unit increase in genetically predicted social isolation and for continuous outcomes this is the mean difference in the outcome per unit increase in genetically predicted social isolation*

Figure 5. Results for social isolation and physical health outcomes



Notes: The points represent the estimated effects, with the horizontal lines indicating the 95% confidence intervals around these estimates. The dotted vertical lines mark the null line, representing the point at which there is no association observed.

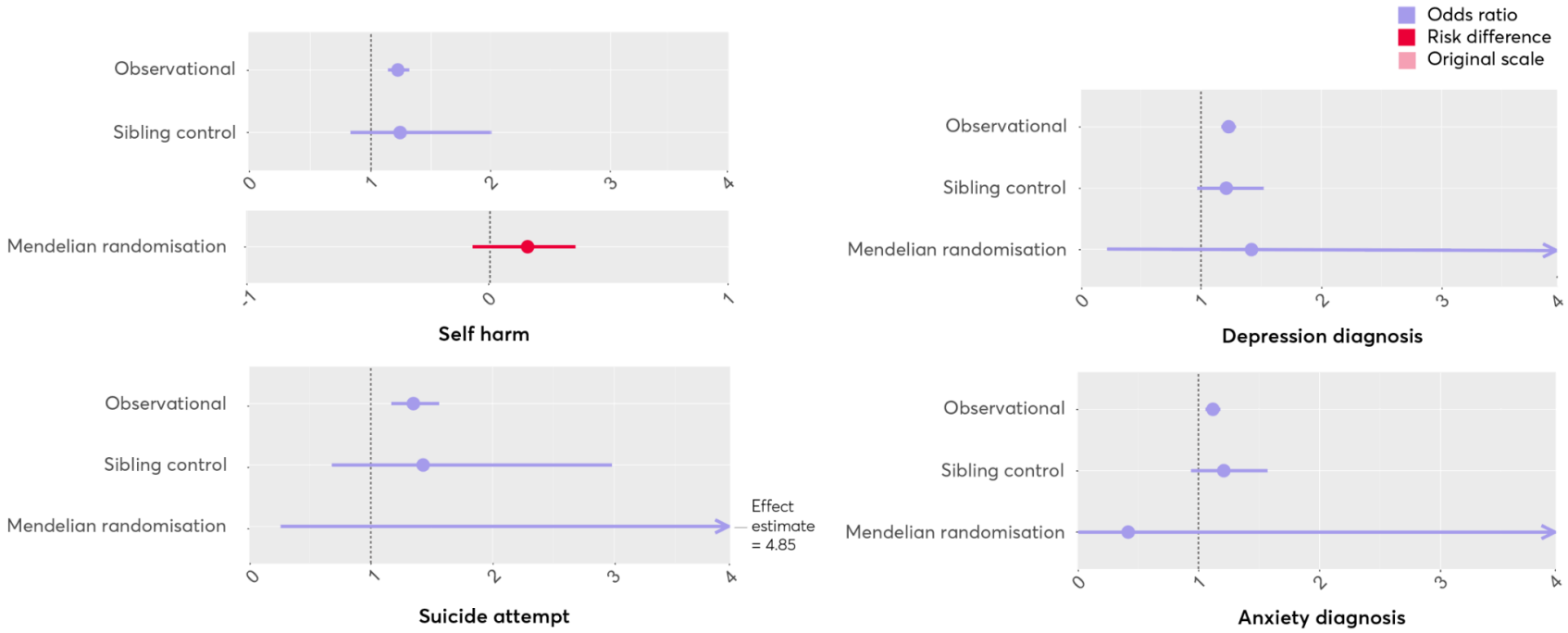
Table 8. Results for social isolation and physical health outcomes

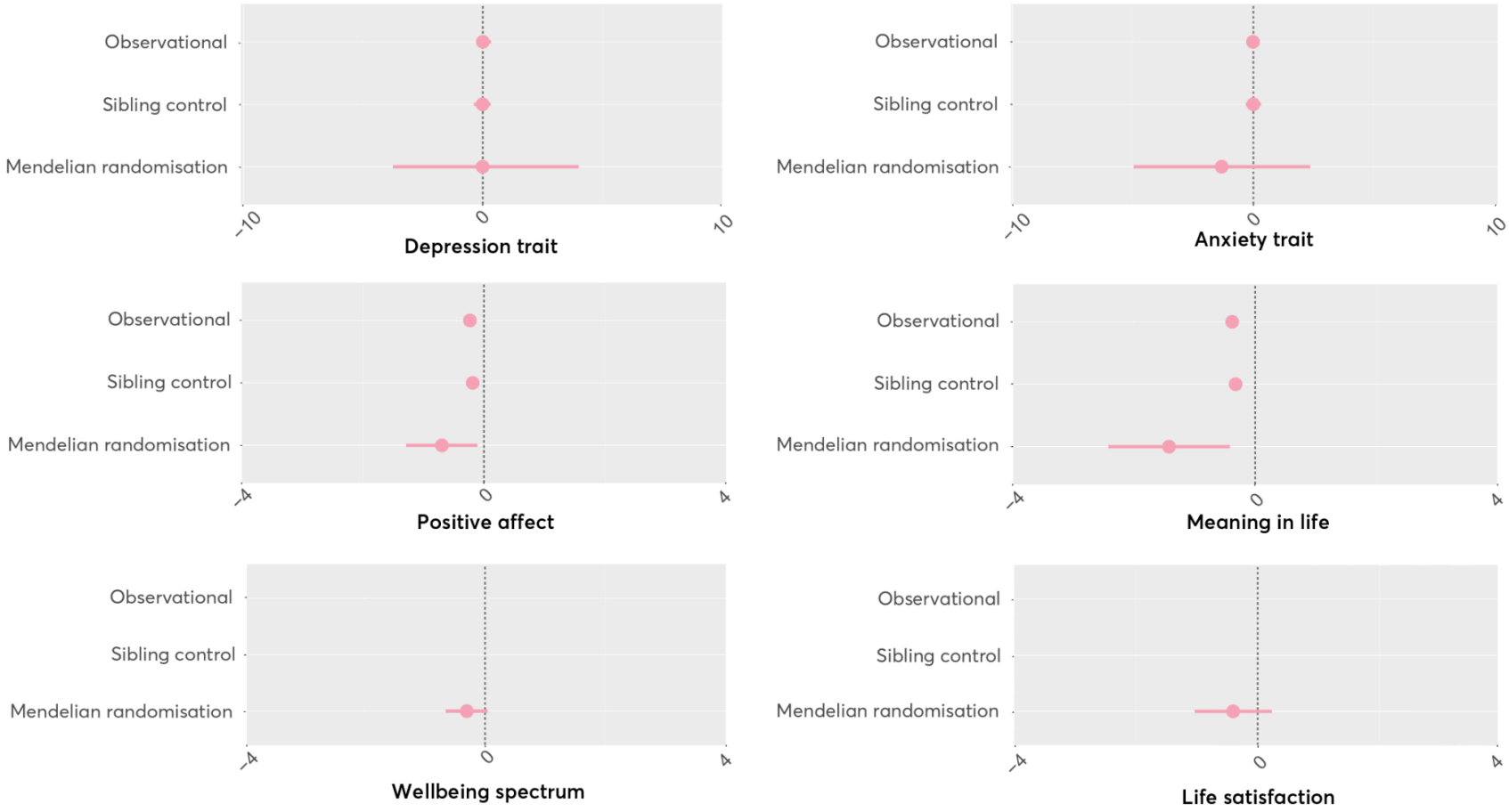
Outcome	Observational		Sibling control		Mendelian randomisation	
	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]
Coronary artery disease	116,512	HR: 0.84 (95% CI: 0.77 to 0.92; p<0.001)	12,090	HR: 0.75 (95% CI: 0.50 to 1.12; p=0.16)	1,347,212	OR: 0.66 (95% CI: 0.25 to 1.79; p=0.42)
Heart failure	119,673	HR: 1.00 (95% CI: 0.84 to 1.19; p=0.98)	33,163	HR: 1.08 (95% CI: 0.78 to 1.50; p=0.65)	977,323	OR: 0.63 (95% CI: 0.18 to 2.22; p=0.48)
Stroke	118,866	HR: 0.97 (95% CI: 0.78 to 1.19; p=0.74)	32,796	HR: 0.96 (95% CI: 0.64 to 1.45; p=0.85)	1,308,460	OR: 1.32 (95% CI: 0.42 to 4.15; p=0.64)
Type 2 diabetes	119,947	OR: 1.22 (95% CI: 1.08 to 1.38; p=0.002)	12,454	OR: 0.94 (95% CI: 0.53 to 1.65; p=0.82)	1,114,458	OR: 0.95 (95% CI: 0.14 to 6.31; p=0.96)
Systolic blood pressure	119,854	0.46 (95% CI: 0.17 to 0.76; p=0.002)	12,449	0.69 (95% CI: -0.65 to 2.03; p=0.31)	757,601	1.80 (95% CI: -10.71 to 14.31; p=0.78)

HR=hazards ratio, OR=odds ratio, CI=confidence intervals

[a] *For continuous outcomes this is an effect estimate on the original scale of the outcome. For systolic blood pressure this is in millimetres of mercury (mmHg).*

Figure 6. Results for social isolation and mental health and wellbeing outcomes





Notes: The points represent the estimated effects, with the horizontal lines indicating the 95% confidence intervals around these estimates. The dotted vertical lines mark the null line, representing the point at which there is no association observed.

Table 9. Results for social isolation and mental health and wellbeing outcomes

Outcome	Observational		Sibling control		Mendelian randomisation	
	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a]	Sample size	Effect estimate (95% CI; p-value)[a,b]
Self-harm	79,596	OR: 1.33 (95% CI: 1.20 to 1.48; p<0.001)	8,228	OR: 1.22 (95% CI: 0.73 to 2.02; p=0.45)	109,291	RD: 0.14 (95% CI: -0.08 to 0.37; p=0.20)
Suicide attempt	79,500	OR: 1.35 (95% CI: 1.17 to 1.56; p<0.001)	8,221	OR: 1.43 (95% CI: 0.68 to 2.98; p=0.35)	518,612	OR: 4.85 (95% CI: 0.26 to 89.71; p=0.29)
Depression diagnosis	119,947	OR: 1.23 (95% CI: 1.17 to 1.29; p<0.001)	12,454	OR: 1.21 (95% CI: 0.97 to 1.52; p=0.10)	142,646	OR: 1.42 (95% CI: 0.22 to 9.21; p=0.72)
Depression trait	78,782	0.25 (95% CI: 0.17 to 0.33; p<0.001)	8,153	0.24 (95% CI: -0.10 to 0.59; p=0.17)	107,790	0.12 (95% CI: -3.75to 4.00; p=0.95)
Anxiety diagnosis	119,947	OR: 1.12 (95% CI: 1.06 to 1.18; p<0.001)	12,454	OR: 1.21 (95% CI: 0.94 to 1.57; p=0.15)	17,526	OR: 0.42 (95% CI: 0.01 to 13.32; p=0.62)

Anxiety trait	79,081	-0.06 (95% CI: -0.14 to 0.007; p=0.08)	8,176	0.003 (95% CI: -0.31 to 0.31; p=0.99)	108,274	-1.29 (95% CI: -4.95 to 2.37; p=0.49)
Wellbeing spectrum	-	-	-	-	2,083,151	-0.30 (95% CI: -0.65 to 0.04; p=0.08)
Positive affect/ happiness	93,483	-0.16 (95% CI: -0.17 to -0.14; p<0.001)	9,561	-0.14 (95% CI: -0.21 to -0.08; p<0.001)	410,603	-0.69 (95% CI: -1.28 to -0.11; p=0.02)
Life satisfaction	-	-	-	-	523,783	-0.40 (95% CI: -1.03 to 0.23; p=0.21)
Meaning in life	78,148	-0.30 (95% CI: -0.32 to -0.28; p<0.001)	8,075	-0.30 (95% CI: -0.38 to -0.22; p<0.001)	107,258	-1.42 (95% CI: -2.42 to -0.42; p=0.005)

OR=odds ratio, RD=risk difference, CI=confidence intervals

[a]*For continuous outcomes this is an effect estimate on the original scale of the outcome. For the depression trait this is a score ranging from 0 to 27, for the anxiety trait this is a score ranging from 0 to 21, for positive affect in UK Biobank this is a rating ranging from 1 to 6, for meaning in life this is a score ranging from 1 to 5.*

[b] *For some binary outcomes this is the approximate risk difference of the outcome per unit increase in genetically predicted social isolation and for continuous outcomes this is the mean difference in the outcome per unit increase in genetically predicted social isolation*

Appendix 5: Observational analysis results tables for different levels of adjustment

Table 10. Observational results with different levels of adjustment for loneliness and general health outcomes

Outcome	Level of adjustment	N	Effect estimate (95% CI)	p-value
Death	unadjusted	414,431	HR: 1.44 (1.40 to 1.48)	<0.001
Death	adjusted1[a]	339,324	HR: 1.41 (1.36 to 1.45)	<0.001
Death	adjusted2[a,b]	332,507	HR: 1.34 (1.30 to 1.39)	<0.001
Multimorbidity	unadjusted	414,329	OR: 2.25 (2.21 to 2.29)	<0.001
Multimorbidity	adjusted1	339,253	OR: 2.14 (2.10 to 2.18)	<0.001
Multimorbidity	adjusted1 with disability	332,439	OR: 1.98 (1.94 to 2.02)	<0.001
Multimorbidity	adjusted1 with ACEs	120,875	OR: 1.94 (1.87 to 2.00)	<0.001
Multimorbidity	adjusted2	118,947	OR: 1.85 (1.78 to 1.91)	<0.001
Hospital admissions	unadjusted	414,432	0.86 (0.74 to 0.97)	<0.001
Hospital admissions	adjusted1	339,325	0.70 (0.58 to 0.81)	<0.001
Hospital admissions	adjusted1 with disability	332,508	0.44 (0.32 to 0.55)	<0.001

Hospital admissions	adjusted1 with ACEs	120,893	0.44 (0.34 to 0.55)	<0.001
Hospital admissions	adjusted2	118,965	0.33 (0.22 to 0.43)	<0.001
Quality-adjusted life years (QALYs)	unadjusted	336,799	-0.05 (-0.05 to -0.05)	<0.001
Quality-adjusted life years (QALYs)	adjusted1	273,910	-0.04 (-0.04 to -0.04)	<0.001
Quality-adjusted life years (QALYs)	adjusted1 with disability	268,055	-0.03 (-0.03 to -0.02)	<0.001
Quality-adjusted life years (QALYs)	adjusted1 with ACEs	94,950	-0.02 (-0.02 to -0.02)	<0.001
Quality-adjusted life years (QALYs)	adjusted2	93,307	-0.01 (-0.02 to -0.01)	<0.001

HR=hazards ratio, OR=odds ratio, CI=confidence intervals, ACEs=adverse childhood events

[a] *For all Cox proportional hazards models the covariate 'centre' (the location where the UK Biobank participant was assessed) not included due to issues with fitting the model*

[b] *For all Cox proportional hazards models with death as an outcome the covariate ACEs was also not included due to issues with fitting the model*

Table 11. Observational results with different levels of adjustment for loneliness and physical health outcomes

Outcome	Level of adjustment	N	Effect estimate (95% CI)	p-value
Coronary artery disease	unadjusted	392,132	HR: 1.27 (1.23 to 1.31)	<0.001
Coronary artery disease	adjusted1[a]	321,985	HR: 1.26 (1.21 to 1.30)	<0.001

Coronary artery disease	adjusted1 with disability[a]	315,593	HR: 1.20 (1.16 to 1.24)	<0.001
Coronary artery disease	adjusted1 with ACEs[a]	117,412	HR: 1.14 (1.06 to 1.23)	<0.001
Coronary artery disease	adjusted2[a]	115,557	HR: 1.10 (1.02 to 1.19)	0.02
Heart failure	unadjusted	412,220	HR: 1.54 (1.48 to 1.60)	<0.001
Heart failure	adjusted1[a]	337,606	HR: 1.52 (1.45 to 1.59)	<0.001
Heart failure	adjusted1 with disability[a]	330,811	HR: 1.40 (1.34 to 1.47)	<0.001
Heart failure	adjusted1 with ACEs[a]	120,617	HR: 1.40 (1.21 to 1.61)	<0.001
Heart failure	adjusted2[a]	118,693	HR: 1.29 (1.12 to 1.50)	<0.001
Stroke	unadjusted	407,082	HR: 1.36 (1.29 to 1.44)	<0.001
Stroke	adjusted1[a]	333,578	HR: 1.37 (1.28 to 1.45)	<0.001
Stroke	adjusted1 with disability[a]	326,922	HR: 1.32 (1.24 to 1.41)	<0.001
Stroke	adjusted1 with ACEs[a]	119,791	HR: 1.13 (0.95 to 1.36)	0.17
Stroke	adjusted2[a]	117,889	HR: 1.11 (0.92 to 1.33)	0.29
Type 2 diabetes	unadjusted	414,432	OR: 1.45 (1.40 to 1.49)	<0.001

Type 2 diabetes	adjusted1	339,325	OR: 1.41 (1.35 to 1.46)	<0.001
Type 2 diabetes	adjusted1 with disability	332,508	OR: 1.15 (1.10 to 1.20)	<0.001
Type 2 diabetes	adjusted1 with ACEs	120,893	OR: 1.25 (1.13 to 1.38)	<0.001
Type 2 diabetes	adjusted2	118,965	OR: 1.04 (0.93 to 1.15)	0.50
Systolic blood pressure	unadjusted	413,588	-2.92 (-3.06 to -2.77)	<0.001
Systolic blood pressure	adjusted1	338,736	-1.61 (-1.76 to -1.45)	<0.001
Systolic blood pressure	adjusted1 with disability	331,948	-1.55 (-1.71 to -1.40)	<0.001
Systolic blood pressure	adjusted1 with ACEs	120,801	-1.54 (-1.81 to -1.28)	<0.001
Systolic blood pressure	adjusted2	118,876	-1.55 (-1.82 to -1.28)	<0.001

HR=hazards ratio, OR=odds ratio, CI=confidence intervals, ACEs=adverse childhood events

[a] For all Cox proportional hazards models the covariate 'centre' (the location where the UK Biobank participant was assessed) was not included due to issues with fitting the model

Table 12. Observational results with different levels of adjustment for loneliness and mental health and wellbeing outcomes

Outcome	Level of adjustment	N	Effect estimate (95% CI)	p-value
Self-harm	unadjusted	131,523	OR: 3.01 (2.85 to 3.19)	<0.001

Self-harm	adjusted1	114,019	OR: 2.43 (2.28 to 2.58)	<0.001
Self-harm	adjusted1 with disability	112,132	OR: 2.28 (2.14 to 2.43)	<0.001
Self-harm	adjusted1 with ACEs	80,247	OR: 1.96 (1.81 to 2.12)	<0.001
Self-harm	adjusted2	79,000	OR: 1.86 (1.72 to 2.02)	<0.001
Suicide attempt	unadjusted	131,343	OR: 3.38 (3.13 to 3.64)	<0.001
Suicide attempt	adjusted1	113,863	OR: 2.62 (2.41 to 2.84)	<0.001
Suicide attempt	adjusted1 with disability	111,982	OR: 2.41 (2.21 to 2.62)	<0.001
Suicide attempt	adjusted1 with ACEs	80,147	OR: 2.02 (1.82 to 2.25)	<0.001
Suicide attempt	adjusted2	78,904	OR: 1.89 (1.70 to 2.11)	<0.001
Depression diagnosis	unadjusted	414,432	OR: 3.15 (3.09 to 3.21)	<0.001
Depression diagnosis	adjusted1	339,325	OR: 2.79 (2.73 to 2.85)	<0.001
Depression diagnosis	adjusted1 with disability	332,508	OR: 2.63 (2.57 to 2.69)	<0.001
Depression diagnosis	adjusted1 with ACEs	120,893	OR: 2.63 (2.53 to 2.72)	<0.001
Depression diagnosis	adjusted2	118,965	OR: 2.54 (2.44 to 2.63)	<0.001

Anxiety diagnosis	unadjusted	414,432	OR: 2.15 (2.11 to 2.21)	<0.001
Anxiety diagnosis	adjusted1	339,325	OR: 1.97 (1.92 to 2.03)	<0.001
Anxiety diagnosis	adjusted1 with disability	332,508	OR: 1.88 (1.83 to 1.93)	<0.001
Anxiety diagnosis	adjusted1 with ACEs	120,893	OR: 1.96 (1.88 to 2.05)	<0.001
Anxiety diagnosis	adjusted2	118,965	OR: 1.90 (1.82 to 1.98)	<0.001
Depression trait	unadjusted	129,518	2.90 (2.82 to 2.97)	<0.001
Depression trait	adjusted1	112,498	2.58 (2.50 to 2.66)	<0.001
Depression trait	adjusted1 with disability	110,678	2.46 (2.39 to 2.54)	<0.001
Depression trait	adjusted1 with ACEs	79,432	2.23 (2.14 to 2.31)	<0.001
Depression trait	adjusted2	78,213	2.14 (2.05 to 2.22)	<0.001
Anxiety trait	unadjusted	130,109	2.24 (2.17 to 2.30)	<0.001
Anxiety trait	adjusted1	112,969	1.96 (1.89 to 2.03)	<0.001
Anxiety trait	adjusted1 with disability	111,146	1.89 (1.82 to 1.96)	<0.001
Anxiety trait	adjusted1 with ACEs	79,741	1.65 (1.57 to 1.73)	<0.001
Anxiety trait	adjusted2	78,513	1.60 (1.52 to 1.68)	<0.001
Happiness	unadjusted	225,943	-0.61 (-0.62 to -0.61)	<0.001
Happiness	adjusted1	189,685	-0.57 (-0.58 to -0.56)	<0.001
Happiness	adjusted1 with disability	186,126	-0.56 (-0.57 to -0.55)	<0.001

Happiness	adjusted1 with ACEs	94,265	-0.53 (-0.54 to -0.51)	<0.001
Happiness	adjusted2	92,761	-0.52 (-0.53 to -0.51)	<0.001
Meaning in life	unadjusted	128,845	-0.51 (-0.52 to -0.49)	<0.001
Meaning in life	adjusted1	111,843	-0.48 (-0.49 to -0.46)	<0.001
Meaning in life	adjusted1 with disability	110,019	-0.47 (-0.48 to -0.45)	<0.001
Meaning in life	adjusted1 with ACEs	78,790	-0.44 (-0.46 to -0.42)	<0.001
Meaning in life	adjusted2	77,577	-0.43 (-0.45 to -0.41)	<0.001

OR=odds ratio, CI=confidence intervals, ACEs=adverse childhood events

Table 13. Observational results with different levels of adjustment for social isolation and general health outcomes

Outcome	Level of adjustment	N	Effect estimate (95% CI)	p-value
Death	unadjusted	412,649	HR: 1.69 (1.63 to 1.76)	<0.001
Death	adjusted1[a]	342,733	HR: 1.34 (1.29 to 1.40)	<0.001
Death	adjusted2[a,b]	335,593	HR: 1.34 (1.29 to 1.40)	<0.001
Multimorbidity	unadjusted	412,549	OR: 1.45 (1.43 to 1.48)	<0.001
Multimorbidity	adjusted1	342,661	OR: 1.07 (1.05 to 1.10)	<0.001
Multimorbidity	adjusted1 with disability	335,524	OR: 1.04 (1.02 to 1.07)	<0.001
Multimorbidity	adjusted1 with ACEs	121,922	OR: 1.06 (1.02 to 1.09)	0.004
Multimorbidity	adjusted2	119,929	1.05 (1.01 to 1.09)	0.02
Hospital admissions	unadjusted	412,650	1.10 (0.99 to 1.21)	<0.001

Hospital admissions	adjusted1	342,734	-0.12 (-0.25 to 0.02)	0.09
Hospital admissions	adjusted1 with disability	335,594	-0.19 (-0.32 to -0.05)	0.006
Hospital admissions	adjusted1 with ACEs	121,940	-0.28 (-0.39 to -0.18)	<0.001
Hospital admissions	adjusted2	119,947	-0.30 (-0.41 to -0.20)	<0.001
Quality adjusted life years (QALYs)	unadjusted	334,902	-0.06 (-0.06 to -0.06)	<0.001
Quality adjusted life years (QALYs)	adjusted1	276,687	-0.004 (-0.007 to -0.002)	<0.001
Quality adjusted life years (QALYs)	adjusted1 with disability	270,553	0.0005 (-0.003 to 0.002)	0.62
Quality adjusted life years (QALYs)	adjusted1 with ACEs	95,783	0.005 (0.003 to 0.008)	<0.001
Quality adjusted life years (QALYs)	adjusted2	94,086	0.006 (0.004 to 0.009)	<0.001

HR=hazards ratio, OR=odds ratio, CI=confidence intervals, ACEs=adverse childhood events

[a] *For all Cox proportional hazards models the covariate 'centre' (the location where the UK Biobank participant was assessed) was not included due to issues with fitting the model*

[b] *For all Cox proportional hazards models with death as an outcome the covariate ACEs was also not included due to issues with fitting the model*

Table 14. Observational results with different levels of adjustment for social isolation and physical health outcomes

Outcome	Level of adjustment	N	Effect estimate (95% CI)	p-value
Coronary artery disease	unadjusted	390,606	HR: 1.13 (1.09 to 1.18)	<0.001
Coronary artery disease	adjusted1[a]	325,212	HR: 0.95 (0.91 to 0.99)	0.02
Coronary artery disease	adjusted1 with disability[a]	318,510	HR: 0.94 (0.90 to 0.98)	0.007
Coronary artery disease	adjusted1 with ACEs[a]	118,431	HR: 0.84 (0.77 to 0.92)	<0.001
Coronary artery disease	adjusted2[a]	116,512	HR: 0.84 (0.77 to 0.92)	<0.001
Heart failure	unadjusted	410,475	HR: 1.43 (1.35 to 1.51)	<0.001
Heart failure	adjusted1[a]	341,000	HR: 1.15 (1.08 to 1.23)	<0.001
Heart failure	adjusted1 with disability[a]	333,885	HR: 1.15 (1.07 to 1.23)	<0.001
Heart failure	adjusted1 with ACEs[a]	121,662	HR: 1.01 (0.85 to 1.20)	0.91
Heart failure	adjusted2[a]	119,673	HR: 1.00 (0.84 to 1.19)	0.98
Stroke	unadjusted	405,408	HR: 1.22 (1.13 to 1.31)	<0.001
Stroke	adjusted1[a]	336,937	HR: 1.03 (0.95 to 1.12)	0.43
Stroke	adjusted1 with disability[a]	329,964	HR: 1.05 (0.96 to 1.13)	0.29
Stroke	adjusted1 with ACEs[a]	120,833	HR: 0.95 (0.77 to 1.17)	0.64

Stroke	adjusted2[a]	118,866	HR: 0.97 (0.78 to 1.19)	0.74
Type 2 diabetes	unadjusted	412,650	OR: 1.71 (1.64 to 1.78)	<0.001
Type 2 diabetes	adjusted1	342,734	OR: 1.12 (1.06 to 1.18)	<0.001
Type 2 diabetes	adjusted1 with disability	335,594	OR: 1.07 (1.01 to 1.13)	0.01
Type 2 diabetes	adjusted1 with ACEs	121,940	OR: 1.25 (1.11 to 1.41)	<0.001
Type 2 diabetes	adjusted2	119,947	OR: 1.22 (1.08 to 1.38)	0.002
Systolic blood pressure	unadjusted	411,812	4.60 (4.43 to 4.77)	<0.001
Systolic blood pressure	adjusted1	342,135	0.11 (-0.07 to 0.29)	0.23
Systolic blood pressure	adjusted1 with disability	335,027	0.13 (-0.05 to 0.31)	0.14
Systolic blood pressure	adjusted1 with ACEs	121,844	0.44 (0.15 to 0.73)	0.003
Systolic blood pressure	adjusted2	119,854	0.46 (0.17 to 0.76)	0.002

HR=hazards ratio, OR=odds ratio, CI=confidence intervals, ACEs=adverse childhood events

[a] For all Cox proportional hazards models the covariate 'centre' (the location where the UK Biobank participant was assessed) was not included due to issues with fitting the model

Table 15. Observational results with different levels of adjustment for social isolation and mental health and wellbeing outcomes

Outcome	Level of adjustment	N	Effect estimate (95% CI)	p-value
Self-harm	unadjusted	131,455	OR: 1.49 (1.38 to 1.62)	<0.001
Self-harm	adjusted1	114,972	OR: 1.61 (1.48 to 1.75)	<0.001
Self-harm	adjusted1 with disability	113,013	OR: 1.57 (1.44 to 1.71)	<0.001
Self-harm	adjusted1 with ACEs	80,890	OR: 1.36 (1.23 to 1.50)	<0.001
Self-harm	adjusted2	79,596	OR: 1.33 (1.20 to 1.48)	<0.001
Suicide attempt	unadjusted	131,270	OR: 1.90 (1.70 to 2.12)	<0.001
Suicide attempt	adjusted1	114,810	OR: 1.76 (1.56 to 1.97)	<0.001
Suicide attempt	adjusted1 with disability	112,857	OR: 1.69 (1.50 to 1.90)	<0.001
Suicide attempt	adjusted1 with ACEs	80,791	OR: 1.39 (1.20 to 1.60)	<0.001
Suicide attempt	adjusted2	79,500	OR: 1.35 (1.17 to 1.56)	<0.001
Depression diagnosis	unadjusted	412,650	OR: 1.42 (1.38 to 1.45)	<0.001
Depression diagnosis	adjusted1	342,734	OR: 1.38 (1.34 to 1.42)	<0.001
Depression diagnosis	adjusted1 with disability	335,594	OR: 1.35 (1.31 to 1.39)	<0.001
Depression diagnosis	adjusted1 with ACEs	121,940	OR: 1.24 (1.18 to 1.30)	<0.001

Depression diagnosis	adjusted2	119,947	OR: 1.23 (1.17 to 1.29)	<0.001
Anxiety diagnosis	unadjusted	412,650	OR: 1.30 (1.26 to 1.34)	<0.001
Anxiety diagnosis	adjusted1	342,734	OR: 1.26 (1.22 to 1.31)	<0.001
Anxiety diagnosis	adjusted1 with disability	335,594	OR: 1.24 (1.20 to 1.29)	<0.001
Anxiety diagnosis	adjusted1 with ACEs	121,940	OR: 1.12 (1.06 to 1.19)	<0.001
Anxiety diagnosis	adjusted2	119,947	OR: 1.12 (1.06 to 1.18)	<0.001
Depression trait	unadjusted	129,422	0.27 (0.20 to 0.33)	<0.001
Depression trait	adjusted1	113,391	0.42 (0.35 to 0.49)	<0.001
Depression trait	adjusted1 with disability	111,508	0.38 (0.31 to 0.45)	<0.001
Depression trait	adjusted1 with ACEs	80,040	0.28 (0.20 to 0.36)	<0.001
Depression trait	adjusted2	78,782	0.25 (0.17 to 0.33)	<0.001
Anxiety trait	unadjusted	129,997	-0.07 (-0.13 to -0.01)	0.02
Anxiety trait	adjusted1	113,874	0.10 (0.04 to 0.16)	0.002
Anxiety trait	adjusted1 with disability	111,980	0.07 (0.007to 0.14)	0.03
Anxiety trait	adjusted1 with ACEs	80,355	-0.05 (-0.12 to 0.03)	0.21
Anxiety trait	adjusted2	79,081	-0.06 (-0.14 to 0.007)	0.08
Happiness	unadjusted	226,040	-0.21 (-0.22 to -0.20)	<0.001
Happiness	adjusted1	191,383	-0.22 (-0.23 to -0.21)	<0.001

Happiness	adjusted1 with disability	187,679	-0.22 (-0.23 to -0.21)	<0.001
Happiness	adjusted1 with ACEs	95,039	-0.16 (-0.18 to -0.15)	<0.001
Happiness	adjusted2	93,483	-0.16 (-0.17 to -0.14)	<0.001
Meaning in life	unadjusted	128,746	-0.33 (-0.35 to -0.32)	<0.001
Meaning in life	adjusted1	112,752	-0.32 (-0.34 to -0.31)	<0.001
Meaning in life	adjusted1 with disability	110,865	-0.32 (-0.34 to -0.30)	<0.001
Meaning in life	adjusted1 with ACEs	79,402	-0.30 (-0.32 to -0.28)	<0.001
Meaning in life	adjusted2	78,148	-0.30 (-0.32 to -0.28)	<0.001

OR=odds ratio, CI=confidence intervals, ACEs=adverse childhood events

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