Risk factors for ongoing symptomatic COVID-19 and post-COVID syndrome in the population: analyses of 10 longitudinal studies and electronic health records in the UK

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Supplementary Table S1. Details of each study

Study Population	Design and Sample Frame	2020 Age Range	Pre-pandemic Survey	Details of Covid surveys (response rate)	Analytic N
Age Homogenous Cohorts					
MCS: Millennium Cohort Study(1,2)	Cohort of UK children born between Sept 2000 and Jan 2002 with regular follow-up surveys from birth.	18-20	2018	Spring 2021 survey response with the issued sample: 33.1%	1055
ALSPAC (G1): Avon Longitudinal Study of Parents and Children-Generation 1(3)	Cohort of children born in the South-West of England between April 1991 and Dec 1992, with regular follow-up surveys from birth. (original young people)	27-29	2017-2018	Three questionnaires: April (19%), June (17.4%), December (26.4%)	668
NS: Next Steps, formerly known as Longitudinal Study of Young People in England(1,4)	Sample recruited via secondary schools in England at around age 13 with regular follow-up surveys thereafter.	29-31	2015	Spring 2021 survey response with the issued sample: 34.3%	848
BCS70: British Cohort Study 1970(1,5)	Cohort of all children born in Great Britain (i.e. England, Wales & Scotland) in one week in 1970, with regular follow-up surveys from birth.	50	2016	Spring 2021 survey response with the issued sample: 45.4%	889
NCDS: National Child Development Study(1,6)	Cohort of all children born in Great Britain (i.e. England, Wales & Scotland) in one week in 1958, with regular follow-up surveys from birth.	62	2013	Spring 2021 survey response with the issued sample: 58.5%	709
Age Heterogeneous Studies					
BIB: Born in Bradford(7,8)	Birth cohort recruiting pregnant women and their children between 2007 and 2011	28-55	2016-2020	Two surveys: April-Jun (30.7%) & Oct-Nov (39.9%)	110
USOC: Understanding Society: the UK Household Longitudinal Survey(9)	A nationally representative longitudinal household panel study, based on a clustered-stratified probability sample of UK households, with all adults aged 16+ in chosen households surveyed annually.	16-96	2018-2019	Seven surveys (full/partial interview): April 2020 (42.0%); May (35.1%); Jun (33.5%); July (32.6%); Sep (30.6%), Nov (28.6%), Jan 2021 (28.5%)	1033
GS: Generation Scotland: the Scottish Family Health Study(10)	A family-structured, population-based Scottish cohort, with participants aged 18-99 recruited between 2006-2011	27-100	2006-2011	Three surveys: April-Jun 2020 (21.3%); Jul-Aug 2020 (15.4%); Feb 2021 (14.3%)	335
ALSPAC(G0): Avon Longitudinal Study of Parents and Children-Generation 0(11)	Parents of the ALSPAC(G1) cohort described above, treated as a separate age-heterogenous study population. (original parents)	45-81	2011-2013	Three questionnaires: April (12.4%), June (12.2%), December (14.3%)	446
TWINSUK: the UK Adult Twin Registry(12,13)	A cohort of UK volunteer adult twins (55% monozygotic and 43% dizygotic) who were sampled between 18-101 years of age.	22-96	2017-2018	Three surveys: April (64.3%), July (77.6%) & November (76.1%)	806

Supplementary Table S2. Ethics and data access statements for each study

NCDS, BCS70, NS and MCS	The most recent sweeps of the NCDS, BCS70, Next Steps and MCS have all been granted ethical approval by the National Health Service (NHS) Research Ethics Committee and all participants have given informed consent. Data for NCDS (SN 6137), BCS70 (SN 8547), Next Steps (SN 5545), MCS (SN 8682) and all four COVID-19 surveys (SN 8658) are available through the UK Data Service.
ALSPAC	Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data. ALSPAC data is available to researchers through an online proposal system. Information regarding access can be found on the ALSPAC website (http://www.bristol.ac.uk/media-library/sites/alspac/documents/researchers/data-access/ALSPAC_Access_Policy.pdf).
BIB	Ethical approval for Born in Bradford was granted by the National Health Service Health Research Authority Yorkshire and the Humber (Bradford Leeds) Research Ethics Committee (reference: 16/YH/0320). Data from the various BiB family studies are available to researchers; see the study website for information on how to access data (https://borninbradford.nhs.uk/research/how-to-access-data/).
USOC	The University of Essex Ethics Committee has approved all data collection for the Understanding Society main study and COVID-19 waves. No additional ethical approval was necessary for this secondary data analysis. All data are available through the UK Data Service (SN 6614 and SN 8644).
GS	Generation Scotland obtained ethical approval from the East of Scotland Committee on Medical Research Ethics (on behalf of the National Health Service). Reference number 20/ES/0021. Access to data is approved by the Generation Scotland Access Committee. See https://www.ed.ac.uk/generation-scotland/for-researchers/access or email access@generationscotland.org for further details.
TWINSUK	All wave of TwinsUK have received ethical approval associated with TwinsUK Biobank (19/NW/0187), TwinsUK (EC04/015) or Healthy Ageing Twin Study (H.A.T.S) (07/H0802/84) studies from NHS Research Ethics Committees at the Department of Twin Research and Genetic Epidemiology, King's College London. The TwinsUK Resource Executive Committee (TREC) oversees management, data sharing and collaborations involving the TwinsUK registry (for further details see https://twinsuk.ac.uk/resources-for-researchers/access-our-data/).

Supplementary Table S3. Descriptives of analytic sample (self-reported COVID-19 symptoms) and the sample excluded from the analysis (no self-reported COVID-19 symptoms)

	MCS		ALSPAC G1		Next Steps		BIB		Usoc		TwinsUK		GS		ALSPAC G0		BCS70		NCDS	
	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded	Analysis sample	Excluded
Sample size	1055	3,293	668	3446	848	3,317	110	488	1033	9267	806	4610	335	2819	446	3890	889	4,815	709	6,063
Age, mean years (SD)	19.9 (0.3)	19.9 (0.3)	28.4	28.4	31.0 (0.3)	31.0 (0.3)	40.7 (5.9)	41.2 (5.7)	48.5 (14.8)	56.4 (16.1)	52.7 (15.85)	59.9 (15.78)	55.9 (10.6)	60.9 (11.5)	58.3 (4.4)	59.5 (4.8)	51 *	51 *	63 *	63 *
Female sex, %	61.8	60.3	63.8	66.6	61.8	62.3	96.4	94.3	65.3	57.5	88	87.8	64.2	63.7	67.9	70.8	57	57.7	54.9	53.4
Ethnicity, %																				
White	81.7	83.3	95.5	95.8	67.7	73.4	44.5	47.3	85.1	89.9	96.2	97.1	96.1	98.3	98.4	98.0	84	85.5	92	91.2
Non-white ethnic minority	18.2	16.2	4.5	4.1	30	24.9	50.9	49.8	13.2	8.7	3.7	2.9	1.5	0.6	1.4	1.9)	3	2.1	2.7	1.4
Missing	0.1	0.6	0	0.1	2.4	1.8	4.6	2.9	1.7	1.4	0.1	0.2	2.4	1.1	0.2	0.1	12.9	12.5	5.4	9.4
Education, %																				
Degree	46.8	39.3	50.6	51.4	49.7	43.3	10	9.6	48.4	39.5	49.9	45.5	48.7	45.1	23.8	26.6	42.4	42.3	40.1	41.3
No degree	47.6	54.8	22.3	24.2	42.2	46.7	74.5	76	41.5	46.7	27.8	41.1	49.3	53.0	68.8	65.5	49.9	50.9	58.5	56.4
Missing	5.6	5.9	27.1	24.4	11.1	10	15.5	14.3	10.1	13.8	22.3	13.4	2.1	1.9	7.4	7.8	7.7	6.9	1.4	2.4
IMD quintile, %																				
1	15.5	18.7	35	34.1	23.7	18.5	45.5	46.3	-	-	7.4	6.3	10.1	6.0	37.7	39.6	11.3	9.1	9.5	8.5
2	15.2	16.5	24.3	23.6	18.5	19.6	30	24.4	-	-	14.6	12.9	11.9	9.7	27.4	24.9	15.1	13.4	15.1	13.8
3	16.9	18.8	15.7	16.7	16.8	18.2	11.8	12.1	-	-	21.1	20.8	15.8	15.1	12.8	14.6	19.2	18.2	17.2	19.7
4	22	19.3	11.8	11.7	17.3	16.9	8.2	8.4	-	-	26.9	26.2	22.7	28.2	9.2	8.8	18.2	21.8	22.4	22.4
5	27.7	23.4	6.9	6.4	12.5	16.7	0.9	3.1	-	-	29.5	33	39.4	41.0	4.3	3.5	23.9	24.7	25.3	26.5
Missing	2.8	3.3	6.3	7.4	11.2	10.1	3.6	5.7	-	-	0.4	0.8	--	--	8.7	8.5	12.4	12.8	10.6	9.1
Occupational class, %																				
Managerial, Admin, Professional	NA	NA	18	14.9	NA	NA	23.6	28.3	38.9	31.1	-	-	52.8	47.3	12.8	11.5	NA	NA	NA	NA
Intermediate	NA	NA	41.9	39.2	NA	NA	32.7	27.7	16.6	16.4	-	-	17.9	17.5	29.2	35.8	NA	NA	NA	NA
Manual/Routine	NA	NA	25.6	31.6	NA	NA	19.1	16.8	21.3	17.4	-	-	11.0	8.2	42.6	38.1	NA	NA	NA	NA
Not in employment	NA	NA	0.3	0.5	NA	NA			20.5	33.6	-	-	0.0	0	1.1	0.7	NA	NA	NA	NA
Missing	NA	NA	14.2	13.8	NA	NA	24.5	27.3	2.7	1.5	-	-	18.2	27.0	14.4	14	NA	NA	NA	NA
Country, %																				
England	70.7	66.4	100	100	97.6	96.5	100	100	83.8	79.9	92.7	91.4	1.2	0.4	100	100	86.6	82.7	86.5	82.1
Scotland	8.8	13.3			0.6	0.6			6	9.5	3.2	4.5	98.8	99.5			6.4	8.5	6.4	8.8
Wales	12.9	11.1			1.1	0.7			6.7	6	3	3.1					5	5	5.4	5.2

Northern Ireland	7.1	8.6			0.1	0.1			3.5	4.6	0.1	0.1	0.0	0			0	0.2	0.3	0.1
Missing	0.5	0.6			0.6	2			0	0	1	0.8					2	0	1.6	3.8
Pre-pandemic mental health, mean scale score (SD)	NA	NA	6.5 (6.2)	6.9 (6.4)	NA	NA	4.3 (5.4)	3.0 (3.8)	12.6 (6.2)	10.8 (5.2)	8.01 (6.13)	7.36 (5.97)	11.8 (6.3)	11.0 (5.4)	7.2 (5.6)	6.3 (5.3)	NA	NA	NA	NA
Pre-pandemic mental health categories, %																				
Yes	15.4	15.8	14.7	17.9	22.2	22.9	10	5.7	28.1	15.8	3.7	51.5	11.6	8.8	13.9	11.3	15	14.3	11.7	11.6
No	79.2	77.6	55.7	54.4	65.1	65.4	67.3	73	69.3	82.6	40.9	3.3	72.8	71.2	65	68.8	16.7	68.4	78.8	78.3
Missing	5.4	6.6	29.6	27.7	12.7	11.7	22.7	21.3	2.6	1.6	55.3	42.5	15.5	20.0	21.1	19.9	16.3	17.3	9.5	10.1
Self-reported health, %																				
Excellent	NA	NA	16.6	14.7	23.9	21.9	5.5	5.7	8.9	9.8	15.5	13.8			16.6	18	16.2	16.4	11.4	13.9
Very Good	NA	NA	36.8	35.7	35.3	36.7	21.8	24.4	32.7	37.9	23.7	26.3			20.2	27.6	30.6	32.6	33.3	34.4
Good	NA	NA	19.6	23.8	20.8	21.7	30.9	35.9	32.5	32.6	16.00%	18.4			30.9	27	26.1	24.2	29.1	29.2
Fair	NA	NA	4.3	5.1	60.5	6.9	13.6	10.2	15.7	13.7	4.8	5.9			7.4	5.5	10.9	10.6	12.7	11.5
Poor	NA	NA	1.3	1.5	1.3	1.8	5.5	2.5	6.1	3.9	1	0.8			2.9	1.4	3.8	3.7	3.8	3.7
Missing	NA	NA	21.3	19.1	12.3	11	22.7	21.3	4.1	2.1	39	34.8			22	20.6	12.4	12.5	9.7	7.4
Pre-pandemic BMI, mean kg/m2 (SD)	23.3 (4.7)	23.2 (4.7)	25.1 (5.3)	24.8 (5.1)	25.4 (5.8)	25.2 (5.3)	26.8 (5.3)	26.0 (5.5)	-	-	26.2 (4.91)	26.7 (5.17)	26.9 (5.6)	26.5 (5.0)	27.2 (4.9)	26.6 (4.8)	28.7 (5.9)	28.2 (5.3)	27.6 (5.0)	27.1 (5.1)
Pre-pandemic BMI categories, %																				
>18.5	4.6	6.9	1.8	2.1	1.5	2.4	1	1.6	-	-	1.4	1.1	1.5	0.7	0.2	0.7	0	0.3	0.5	0.5
18.5 - 24.9999	63.5	59.6	41	39.0	46.9	47.9	31.8	40.4	-	-	19.7	26.1	32.5	34.1	2	26.5	22.8	24.3	26.8	31.9
25 – 29.9999	15.5	16.6	16.5	16.3	21.7	20.9	21.8	22.7	-	-	16.5	20.4	33.7	28.7	25.3	25	29.7	29.3	35.3	35.6
30+	8.7	8.4	10.3	8.9	13.6	14	20.9	16.4	-	-	8.9	10.8	16.4	16.3	13.9	12.8	27.3	25.7	22.7	19.4
Missing	7.7	8.6	30.4	33.7	16.3	14.8	24.5	18.9	-	-	53.5	41.6	15.8	20.3	38.6	35	20.1	20.4	14.7	12.6
Diabetes, %																				
No	NA	NA	67.8	66.5	NA	NA	NA	NA	93	92	65.1	64.9	82.4	78.5	76.9	77.2	84.5	84.6	83.4	87.7
Yes	NA	NA	0.3	0.4	NA	NA	5.5	3.9	7	8	1.7	3.1	2.1	1.5	1.1	2.3	3.2	2.9	6.8	4.9
Missing	NA	NA	31.9	33.1	NA	NA	94.5	96.1	-	-	33.1	31.9	15.5	20.0	22	20.5	12.4	12.5	9.9	7.5
Hypertension, %																				
No	NA	NA	67.2	65.6	NA	NA	NA	NA	79.7	74.1	60.9	57.6	77.3	69.4	65.5	70.3	NA	NA	69	73.6
Yes	NA	NA	0.8	1.2	NA	NA	12.7	5.9	20.3	25.9	12.5	19.7	7.2	10.6	15.3	13.1	NA	NA	21.3	19.9
Missing	NA	NA	32.0	33.2	NA	NA	87.3	94.1	-	-	26.6	22.7	15.5	20.0	19.3	16.6	NA	NA	9.7	7.5
High cholesterol, %																				
No	NA	NA	67.1	63.5	NA	NA	Na	NA	-	-	58.4	57.6			52	54.9	NA	NA	NA	NA
Yes	NA	NA	0	0.1	NA	NA	1.8	1.8	-	-	15.1	23.2			6.5	7.6	NA	NA	NA	NA
Missing	NA	NA	32.9	36.4	NA	NA	98.2	98.2	-	-	26.4	22.2			41.5	37.5	NA	NA	NA	NA
Asthma, %																				
No	74.7	76.2	49.4	49.7	NA	NA	NA	NA	78.9	85.3	7.3	10.6	70.7	72	65.7	68	78	77.3	80.5	81.8
Yes	10.9	10.2	18	17.1	NA	NA	10.9	12.3	21.1	14.7	7.2	7.9	13.7	8.1	11.7	11.2	9.7	10.2	9.6	10.7

Missing	14.4	13.6	32.6	33.2	NA	NA	89.1	87.7	-	-	85.5	81.6	15.5	20.0	22.7	20.8	12.4	12.5	9.9	7.5
Current smoker, %																				
No	43.2	48.7	49.4	49.7	64.4	61.2	84.5	83.2	91.5	92.2	85.9	88.5	93.4	94.6	57.2	61.1	72.4	69	79	77.8
Yes	11.8	8.4	18	17.1	8	10.1	5.5	6.6	8.4	7.8	13.8	10.7	5.7	4.8	28.3	26.2	7.3	10	4.5	7.5
Missing	45	42.9	32.63	33.2	27.6	28.7	10	10.2	0.1	0.0	0.4	0.8	0.9	0.6	14.6	12.7	20.3	21	16.5	14.7

Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland: the Scottish Family Health Study); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC); BiB (Born in Bradford). Unweighted data. Note. * SD values for age are approximately zero for these cohorts. All participants in NCDS and BCS70 were born in the same week in 1958 and 1970, respectively

Supplementary Table S4. Length of time of symptoms (using self-report direct measures) by COVID-19 status (confirmed infection vs self-report).

	Mean age	COVID-19 ascertainment	N with symptom duration data	Duration of symptoms, N (%)		
				Acute (0-4 weeks)	Ongoing symptomatic COVID-19 (4-12 weeks)	Post COVID-19 syndrome (12+ weeks)
MCS	19.9	***Confirmed***	***552***	***532 (96.4)***	***15 (2.7)***	***5 (0.9)***
		Suspected	503	478 (95.0)	17 (3.4)	8 (1.6)
ALSPAC G1	28.4	***Confirmed***	***187***	***144 (77.0)***	***25 (13.4)***	***18 (9.6)***
		Suspected	481	375 (78.0)	15 (22.0)	34 (7.1)
Next Steps	31	***Confirmed***	***400***	***360 (90.0)***	***26 (6.5)***	***14 (3.5)***
		Suspected	448	413 (92.2)	25 (5.6)	10 (2.2)
BCS70	51	***Confirmed***	***386***	***316 (81.9)***	***50 (13.0)***	***20 (5.2)***
		Suspected	503	441 (87.7)	34 (6.8)	28 (5.6)
TwinsUK	52.7	***Confirmed***	***377***	***261 (69.2)***	***66 (17.57)***	***50 (13.3)***
		Suspected	429	318 (74.1)	80 (18.6)	31 (7.2)
GS	55.9	***Confirmed***	***83***	***51 (61.4)***	***19 (22.9)***	***13 (15.7)***
		Suspected	252	173 (67.7)	35 (13.9)	44 (17.5)
ALSPAC G0	58.3	***Confirmed***	***95***	***73 (76.8)***	***17 (17.9)***	***5 (5.3)***
		Suspected	351	229 (65.2)	51 (14.5)	71 (20.2)
NCDS	63	***Confirmed***	***313***	***248 (79.2)***	***49 (15.7)***	***16 (5.1)***
		Suspected	396	330 (83.3)	48 (12.1)	18 (4.6)
BiB	40.7	***Confirmed***	***34***	***22 (64.7)***	***8 (23.5)***	***4 (11.8)***
		Suspected	76	18 (23.7)	17 (22.4)	41 (53.9)

Note. *Confirmed*: tested positive by PCR, antigen and/or antibody test; Suspected: strong personal suspicion and/or medical advice of COVID-19, but no test result to confirm. Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland: The Scottish Family Health Study); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC); BiB (Born in Bradford).

Supplementary Table S5. Length of time of symptoms by COVID-19 infection (swab/saliva and antibody test)

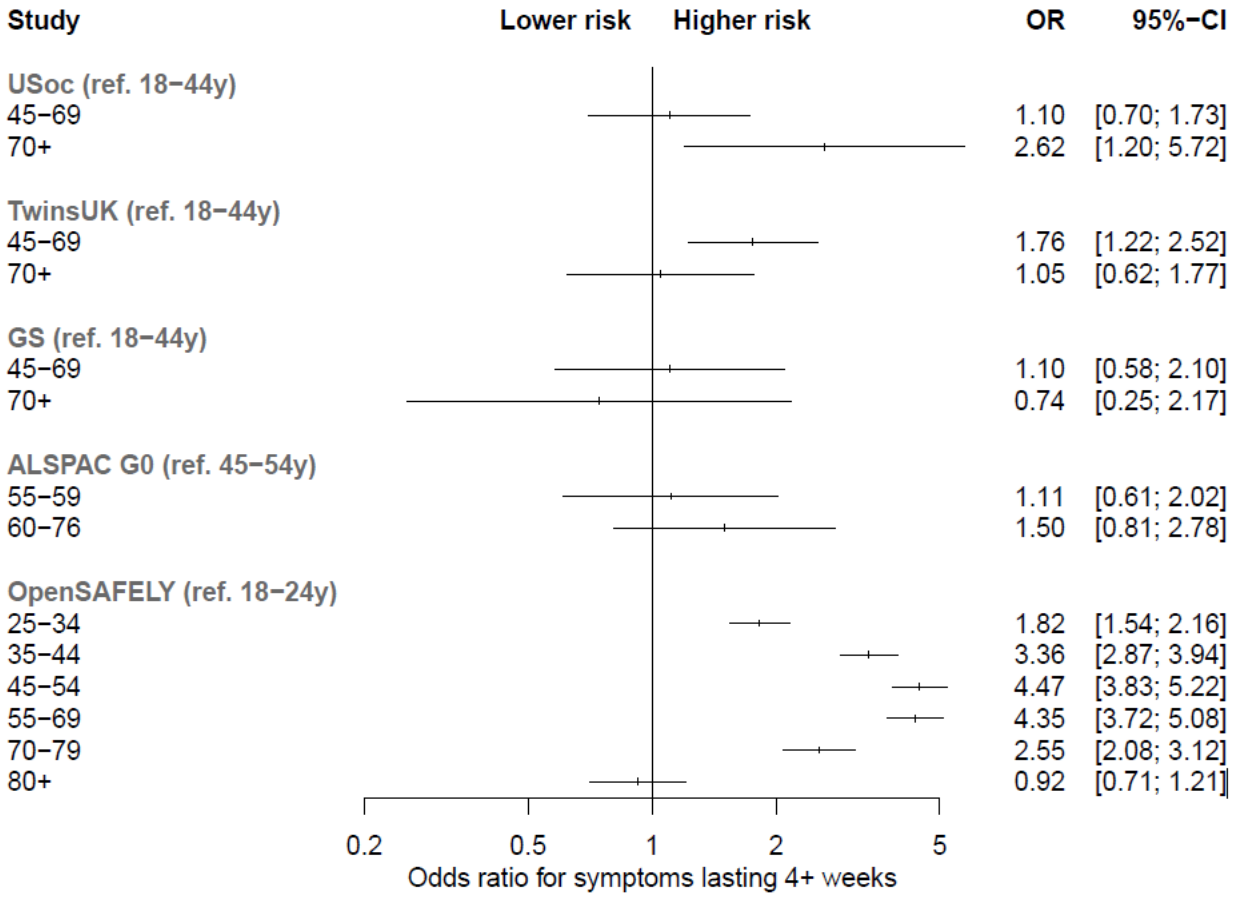
	COVID-19 ascertainment	N with symptom duration data	Duration of symptoms, N (%)		
			Acute (0-4 weeks)	Ongoing symptomatic COVID-19 (4-12 weeks)	Post COVID-19 syndrome (12 + weeks)
ALSPAC G1	Symptomatic test positive (antibody or PCR) and self-diagnosed	***193 (100)***	***150 (78)***	***21 (11)***	***22 (11)***
	Symptomatic test negative (antibody or PCR) and self-diagnosed	282 (100)	215 (78)	45 (16)	22 (8)
TwinsUK	Symptomatic test positive (antibody or PCR) and self-diagnosed	***377(100)***	***261 (69.2)***	***66 (17.57)***	***50 (13.3)***
	Symptomatic test negative (antibody or PCR) and self-diagnosed	429 (100)	318 (74.1)	80 (18.6)	31 (7.2)
ALSPAC G0	Symptomatic test positive (antibody or PCR) and self-diagnosed	***57(100)***	***44 (77.2)***	***5 (8.8)***	***8 (14)***
	Symptomatic test negative (antibody or PCR) and self-diagnosed	202 (100)	131 (64.9)	39 (19.3)	32 (15.8)
BiB	Symptomatic test positive (antibody or PCR) and self-diagnosed	***35 (100)***	***23 (65.7)***	***8 (22.9)***	***4 (11.4)***
	Symptomatic test negative (antibody or PCR) and self-diagnosed	42 (100)	6 (14.3)	9 (21.4)	27 (64.3)

Sources: ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC); BiB (Born in Bradford).

Supplementary Table S6. Length of time of symptoms (using sum of individual symptoms) by COVID-19 status (BIB; TwinsUK)

	COVID-19 ascertainment	N with symptom duration data	Duration of symptoms, N (%)		
			Acute (0-4 weeks)	Ongoing symptomatic COVID-19 (4-12 weeks)	Post COVID-19 syndrome (12+ weeks)
TwinsUK	Not Confirmed	4611	820 (17.8)	1006 (21.8)	1328 (28.8)
	Confirmed	***363***	***87 (24)***	***104 (28.7)***	***139 (38.3)***
	Suspected	696	185 (26.6)	142 (20.4)	296 (42.5)
BiB	***Confirmed***	***34***	***22 (64.7)***	***8 (23.5)***	***4 (11.8)***
	Suspected	76	18 (23.7)	17 (22.4)	41 (53.9)

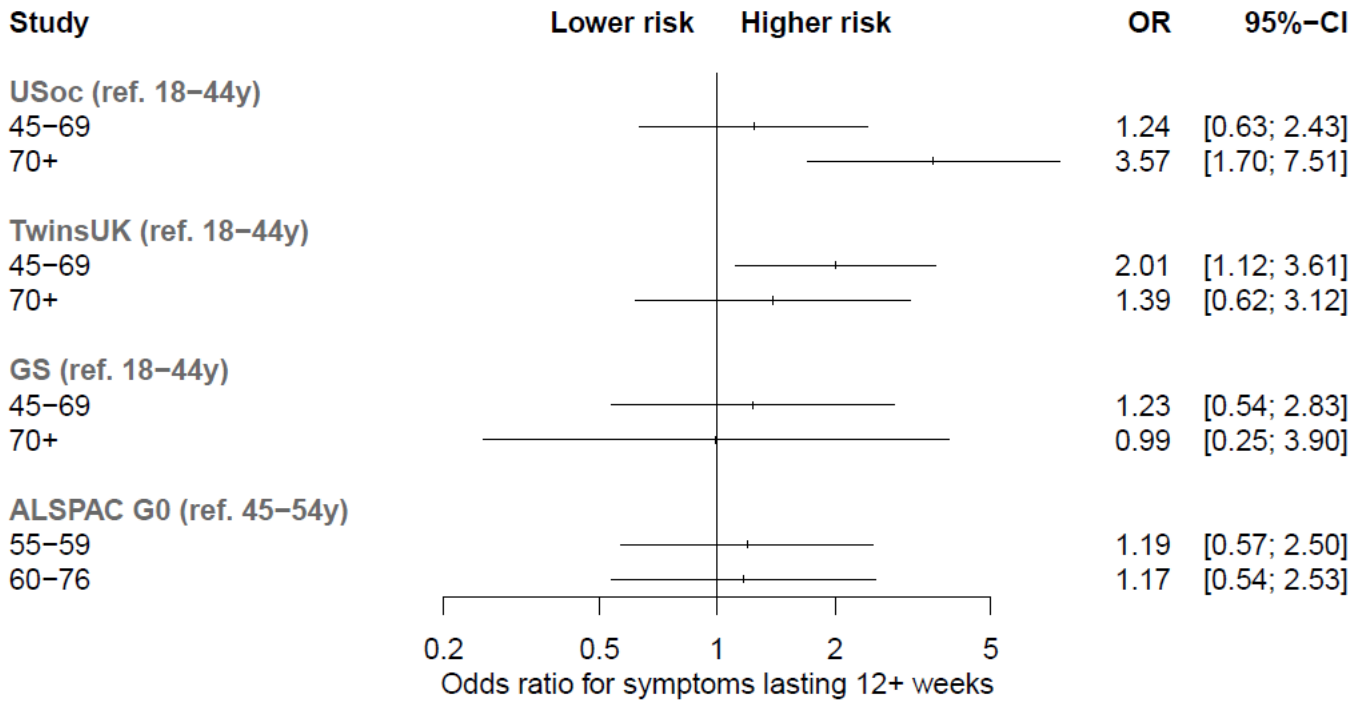
Supplementary figure 1: Categorical age associations with symptoms 4+ week in the sub-set of the longitudinal studies that are heterogeneous in age and EHRs from OpenSAFELY



Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate.

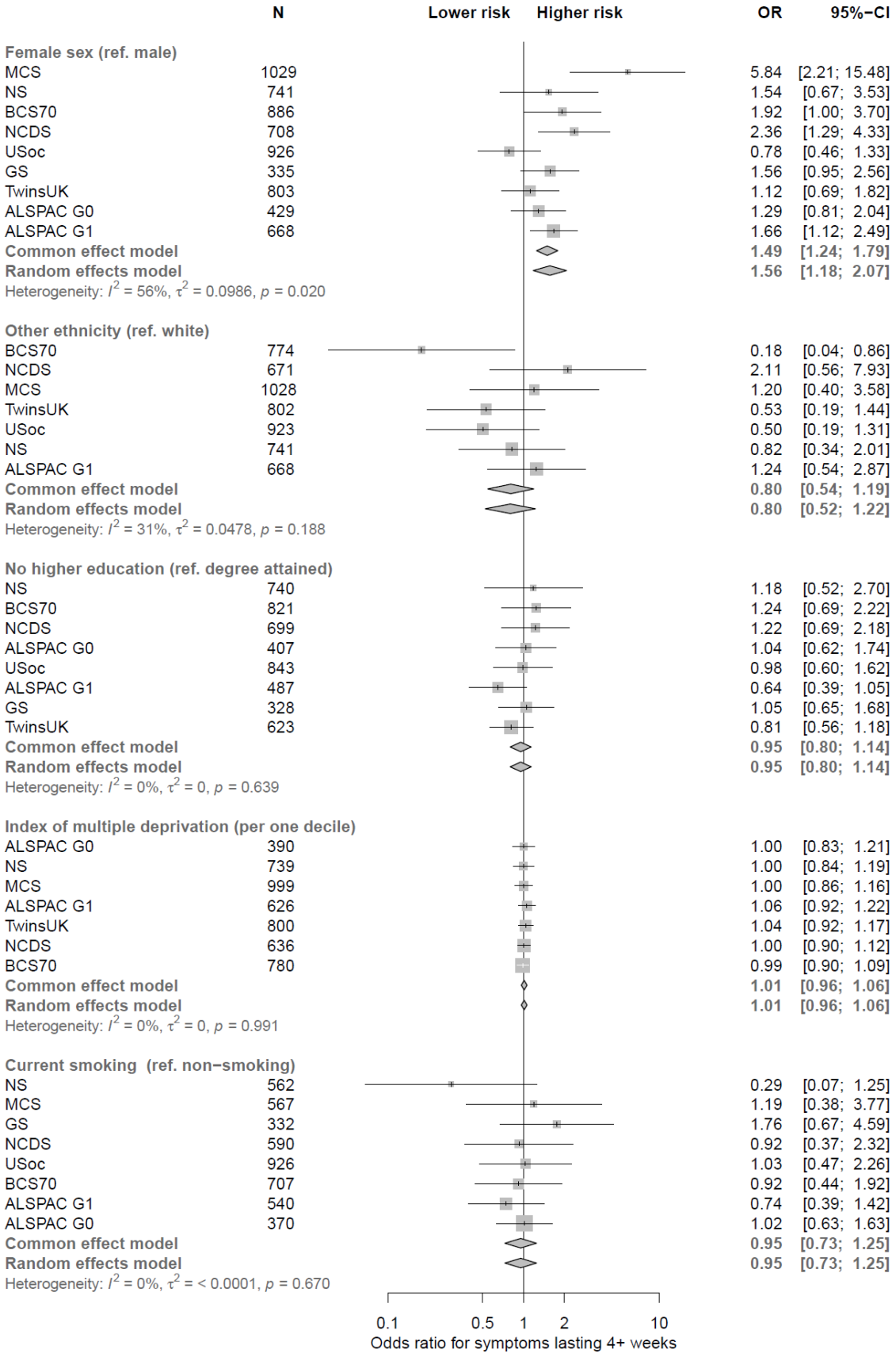
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland: The Scottish Family Health Study); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Usoc *N* = 1033, TwinsUK *N* = 806, GS *N* = 335, ALSPAC G0 *N* = 446, OpenSAFELY *N* = 4,189

Supplementary figure 2: Categorical age associations with symptoms 12+ week in the sub-set of the longitudinal studies that are longitudinal in age



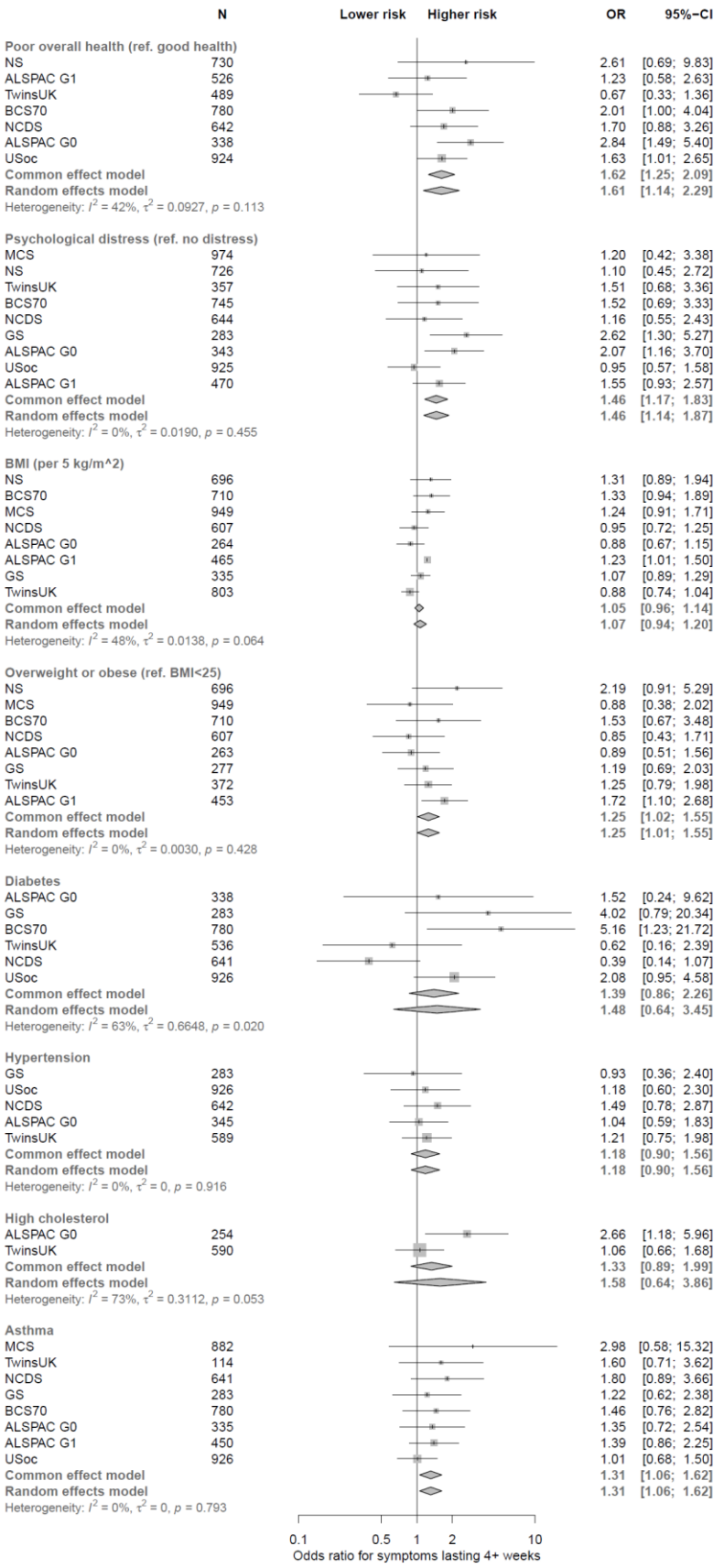
Sources: USoc (Understanding Society); GS (Generation Scotland: the Scottish Family Health Study); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Usoc *N* = 1033, TwinsUK *N* = 806, GS *N* = 335, ALSPAC G0 *N* = 446.

Supplementary figure 3: Meta-analysis results for sociodemographic characteristics with symptoms for 4+ weeks in the longitudinal studies



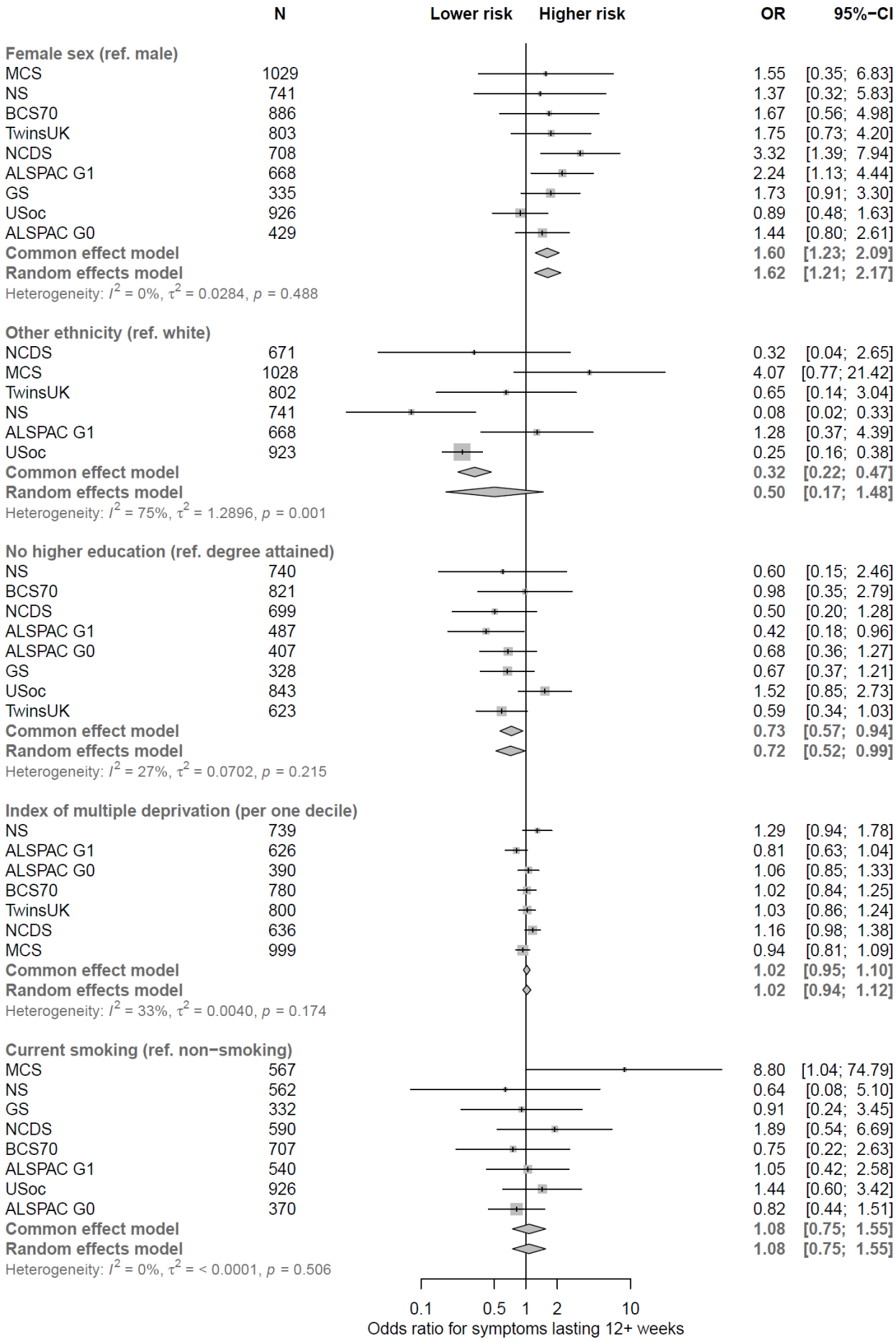
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random-effect meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for continuous age and sex, except where sex is the risk factor (only adjusted for age).

Supplementary figure 4: Full meta-analysis results for health factors with symptoms for 4+ weeks in the longitudinal studies



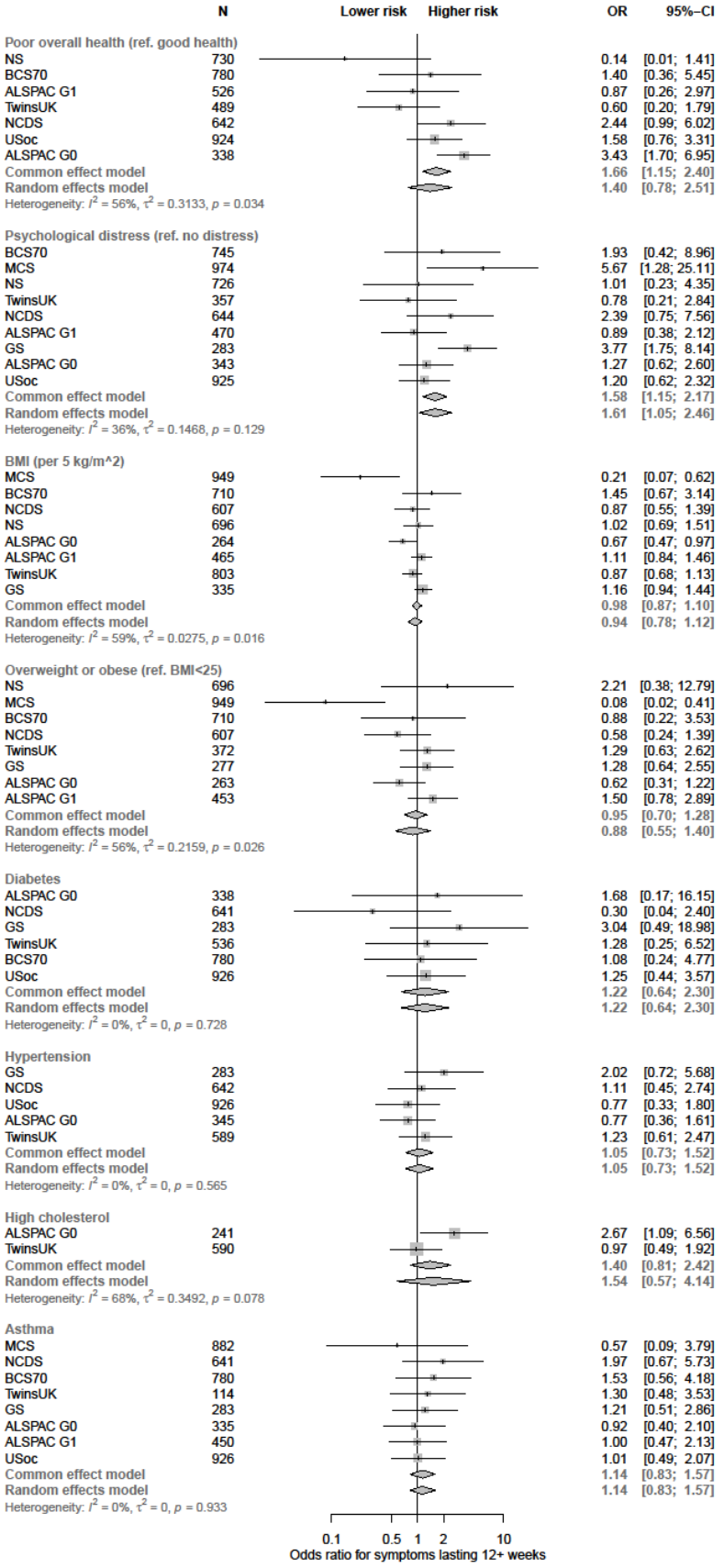
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). The reference category for 'Diabetes', 'Hypertension', 'High Cholesterol', and 'Asthma' is the absence of condition. Estimates from fixed and random-effect meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex.

Supplementary figure 5: Full meta-analysis results for sociodemographic characteristics with symptoms for 12+ weeks in the longitudinal studies



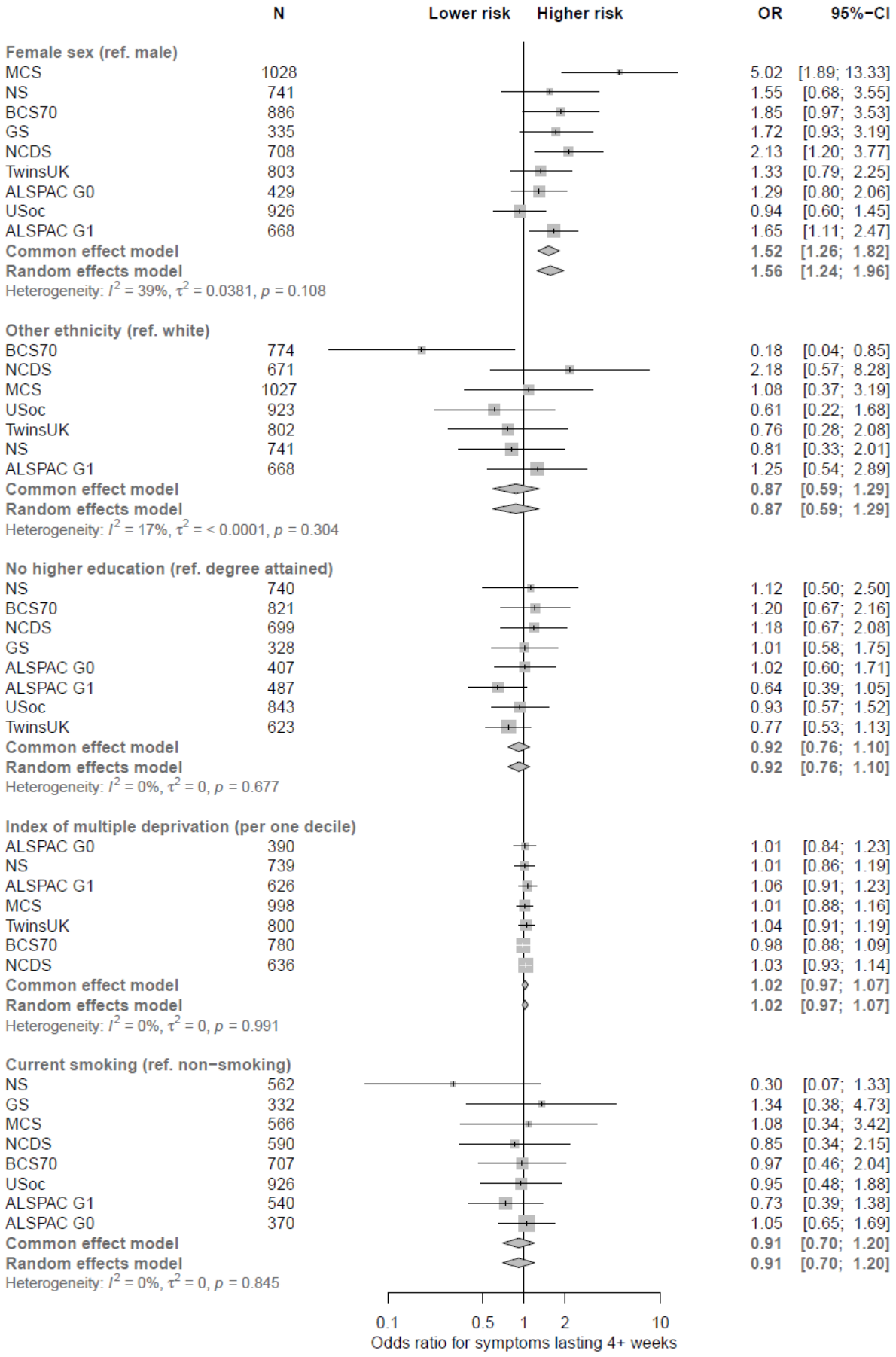
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex, where relevant.

Supplementary figure 6: Full meta-analysis results for health factors with symptoms for 12+ weeks in the longitudinal studies



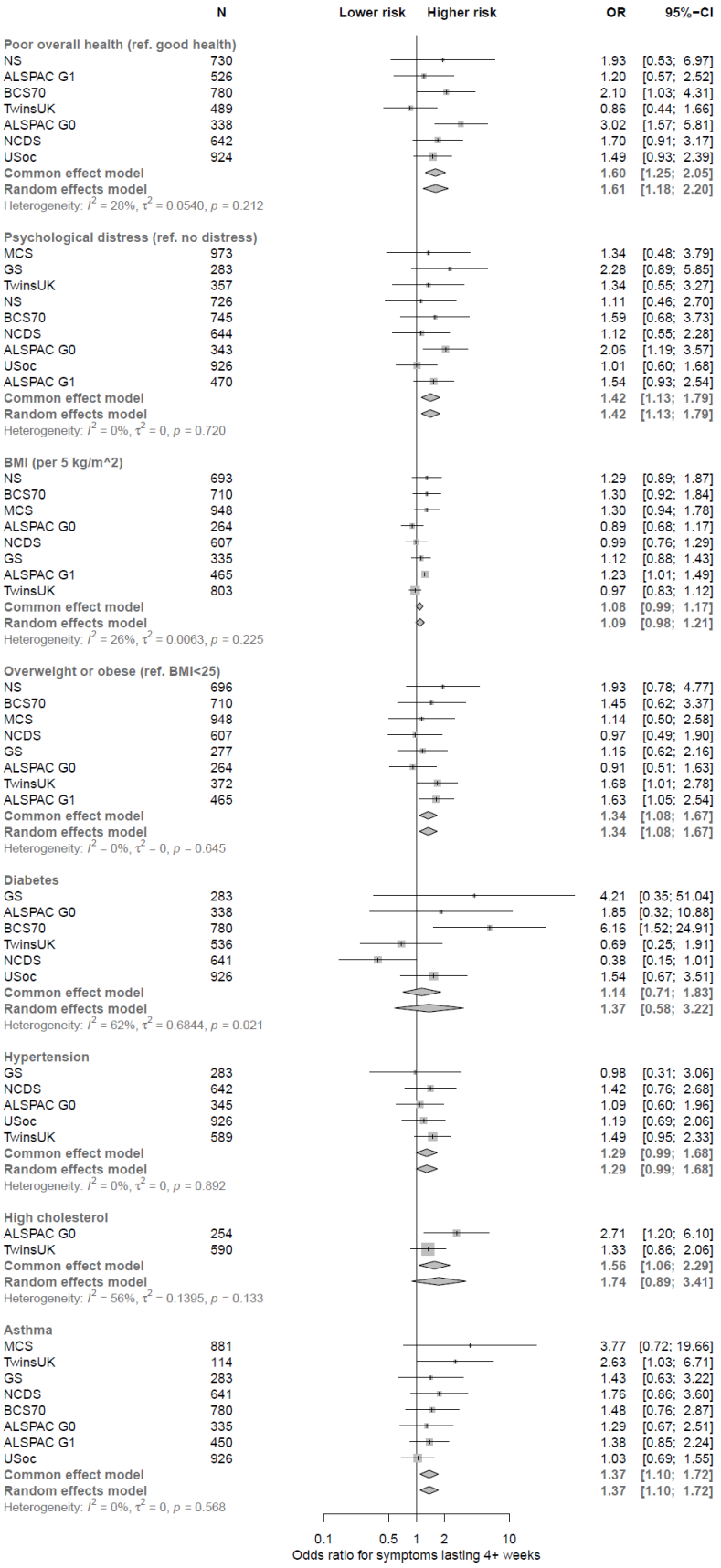
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). The reference category for 'Diabetes', 'Hypertension', 'High Cholesterol', and 'Asthma' is the absence of condition. Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex.

Supplementary figure 7: Secondary meta-analysis results for sociodemographic characteristics with symptoms for 4+ weeks in the longitudinal studies, including inverse probability weights for COVID-19 risk



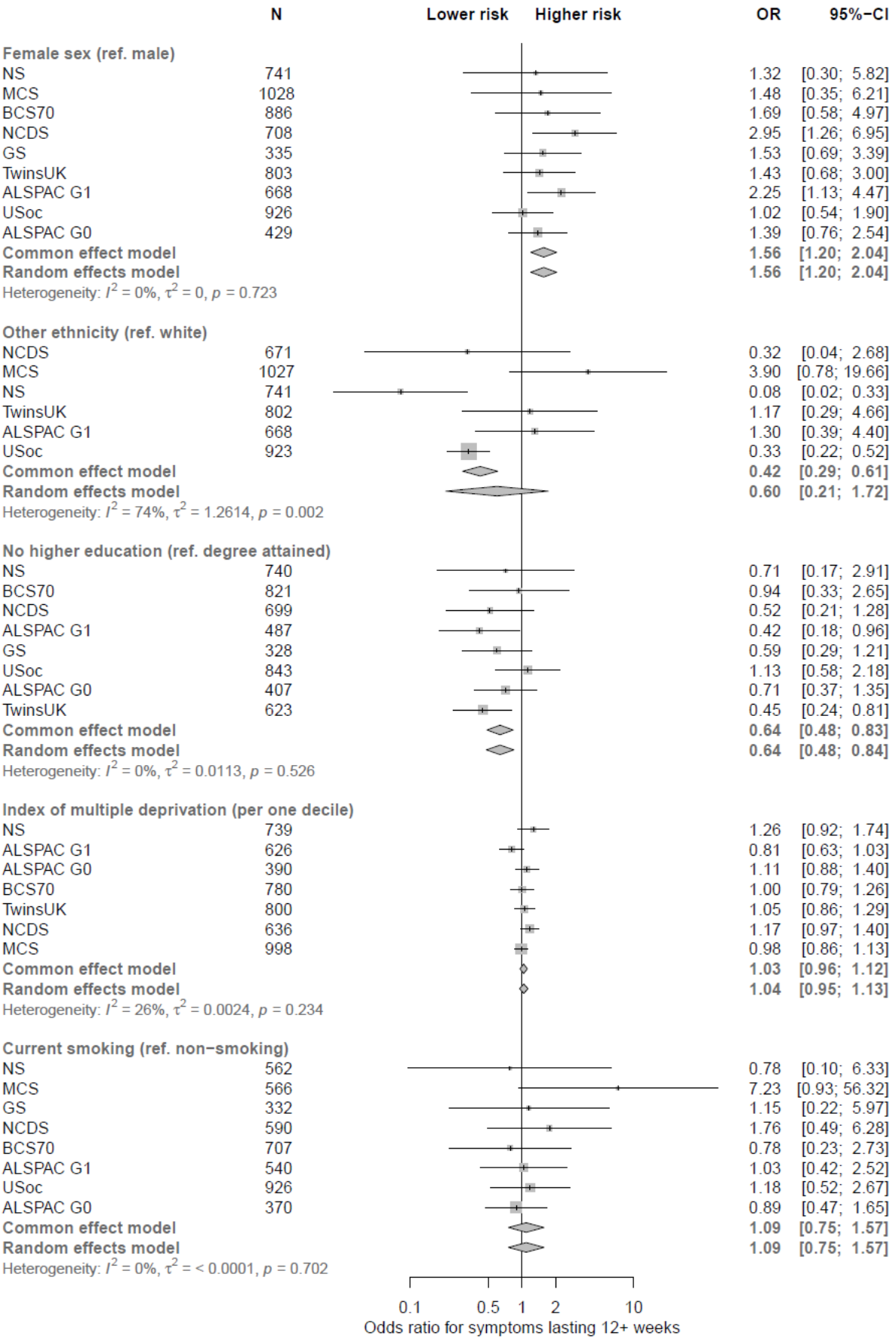
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex.

Supplementary figure 8: Secondary meta-analysis results for health factors with symptoms for 4+ weeks in the longitudinal studies, including inverse probability weights for COVID-19 risk



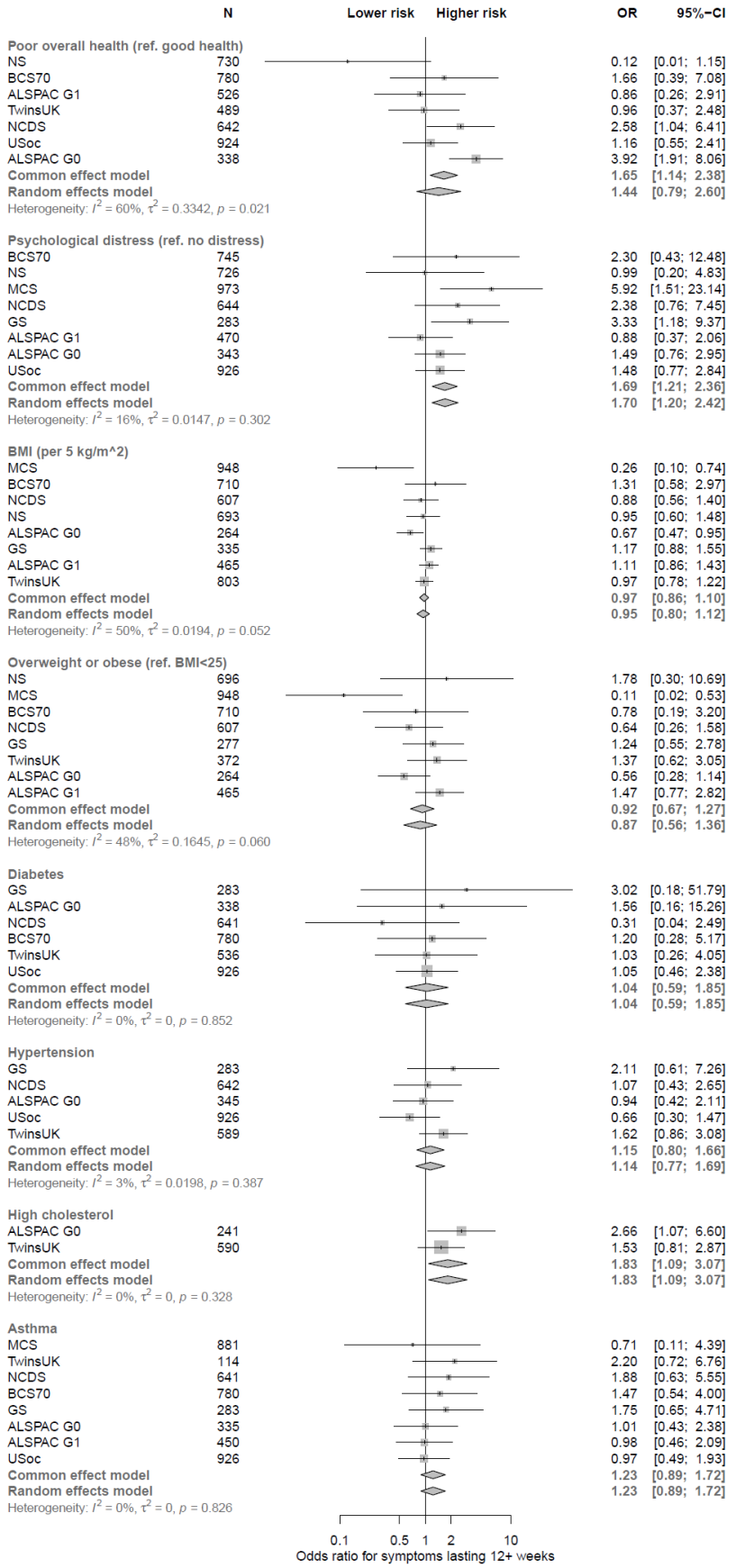
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). The reference category for 'Diabetes', 'Hypertension', 'High Cholesterol', and 'Asthma' is the absence of condition. Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex.

Supplementary figure 9: Secondary meta-analysis results for sociodemographic characteristics with symptoms for 12+ weeks in the longitudinal studies, including inverse probability weights for COVID-19 risk



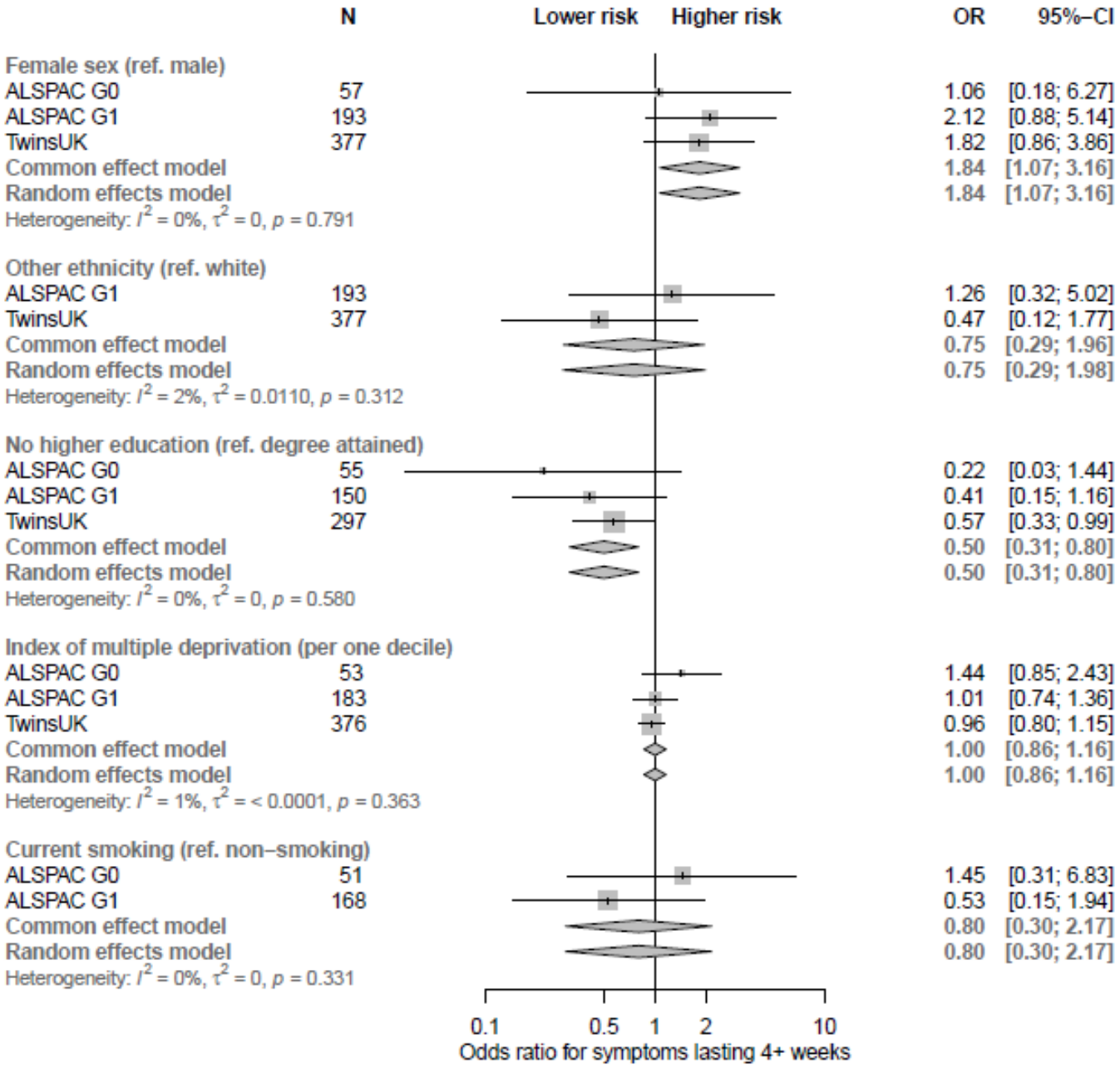
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex.

Supplementary figure 10: Secondary meta-analysis results for health traits with symptoms for 12+ weeks in the longitudinal studies, including inverse probability weights for COVID-19 risk



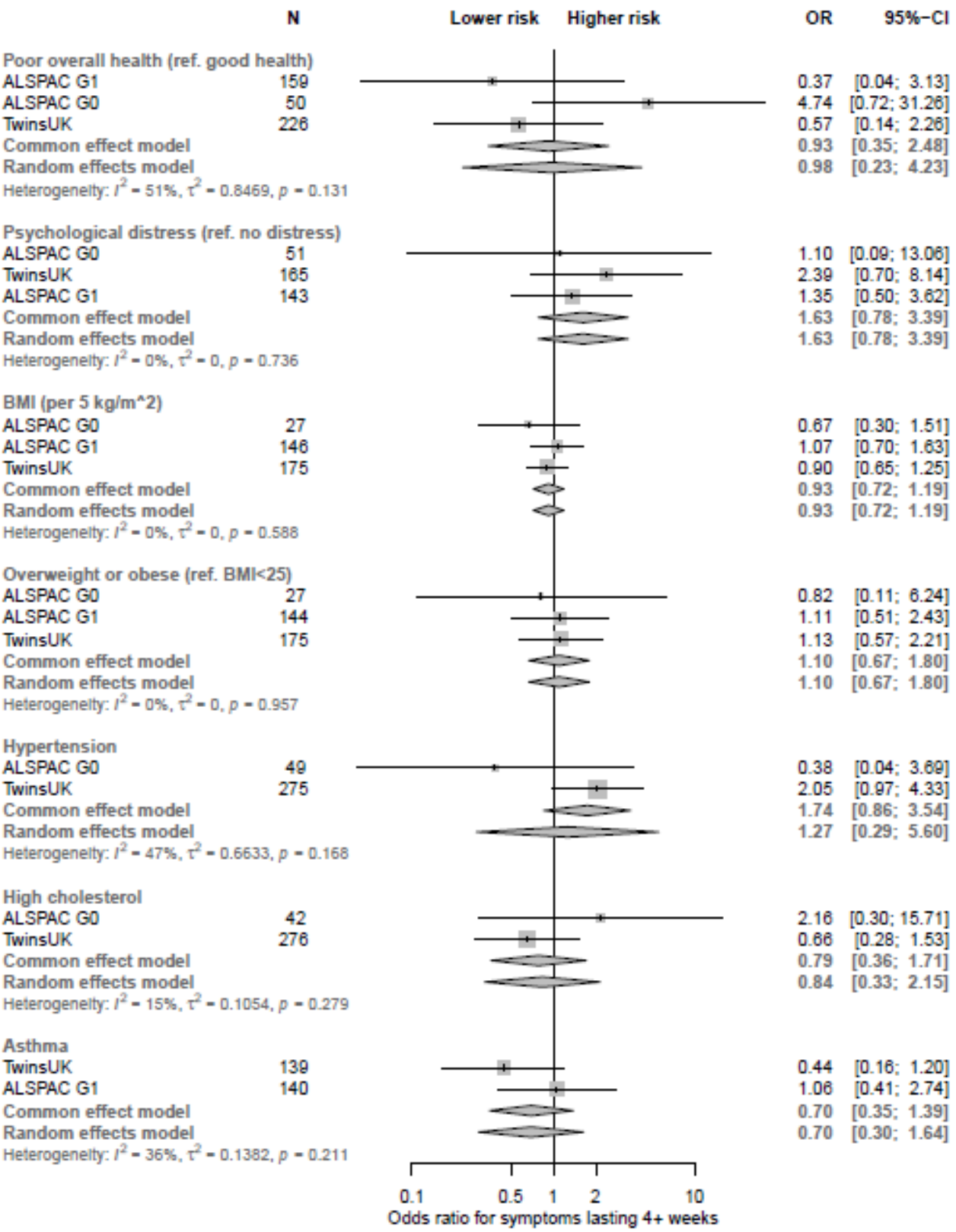
Sources: MCS (Millennium Cohort Study); ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); NS (Next Steps); BCS 70 (1970 British Cohort Study), NCDS (National Child Development Study); USoc (Understanding Society); GS (Generation Scotland); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). The reference category for 'Diabetes', 'Hypertension', 'High Cholesterol', and 'Asthma' is the absence of condition. Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Associations adjusted for age and sex.

Supplementary figure 11: Sub-group meta-analysis results for sociodemographic characteristics with symptoms for 4+ weeks in individuals with COVID-19 status confirmed by a positive PCR test and/or serology result



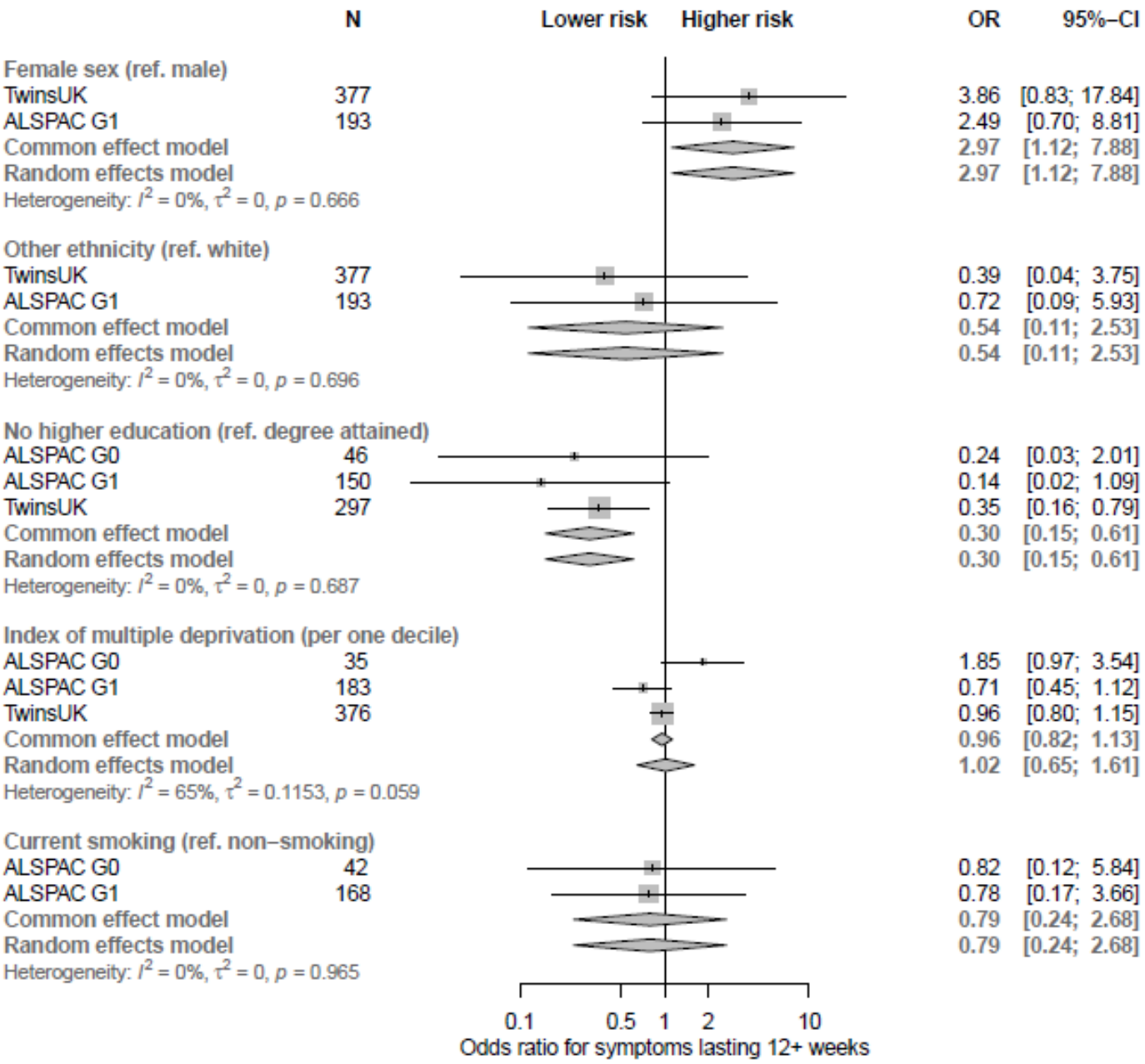
Sources: ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Adjusted for age, sex and ethnicity, where relevant. Some samples were omitted from specific risk factor long COVID analyses, where sample sizes were too small to contribute, e.g., ALSPAC G0 in the ethnicity meta-analysis.

Supplementary figure 12: Sub-group meta-analysis results for health traits with symptoms for 4+ weeks in individuals with COVID-19 status confirmed by a positive PCR test and/or serology result



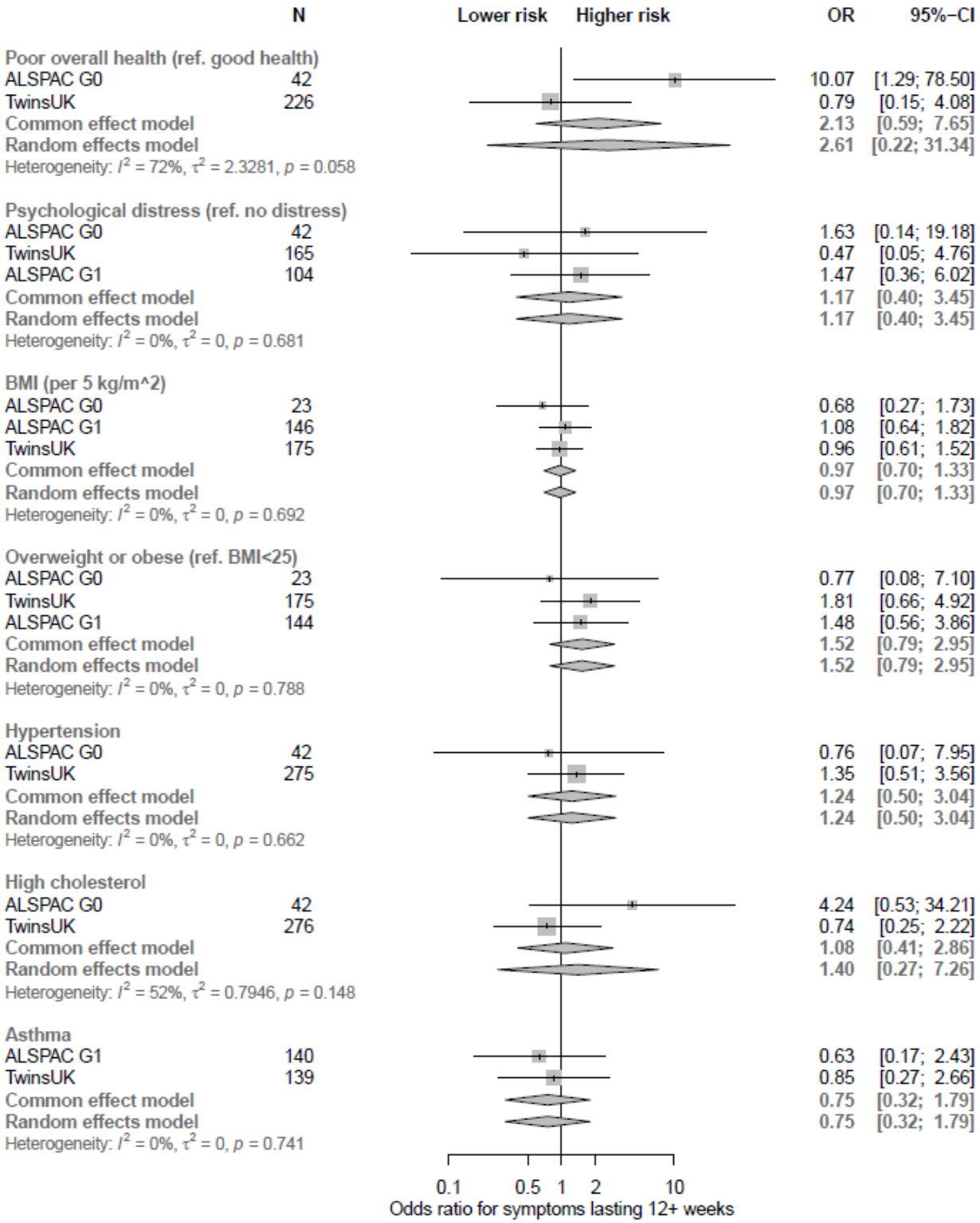
Sources: ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). The reference category for 'Diabetes', 'Hypertension', 'High Cholesterol', and 'Asthma' is the absence of condition. Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Adjusted for age, sex and ethnicity. Some samples were omitted from specific risk factor long COVID analyses, where sample sizes were too small to contribute, e.g., ALSPAC G0 in the asthma meta-analysis.

Supplementary figure 13: Sub-group meta-analysis results for sociodemographic characteristics with symptoms for 12+ weeks in individuals with COVID-19 status confirmed by a positive PCR test and/or serology result



Sources: ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Adjusted for age, sex and ethnicity, where relevant. Some samples were omitted from specific risk factor long COVID analyses, where sample sizes were too small to contribute, e.g., ALSPAC G0 in the ethnicity meta-analysis.

Supplementary figure 14: Sub-group meta-analysis results for health traits with symptoms for 12+ weeks in individuals with COVID-19 status confirmed by a positive PCR test and/or serology result



Sources: ALSPAC G1 (Children of the Avon Longitudinal Study of Parents and Children); TwinsUK (UK Adult Twin Registry); ALSPAC G0 (parents of ALSPAC). The reference category for 'Diabetes', 'Hypertension', 'High Cholesterol', and 'Asthma' is the absence of condition. Estimates from fixed and random effects meta-analyses are presented as odds ratios (OR) and 95% confidence intervals (CIs) as appropriate. Adjusted for age, sex, and ethnicity. Some samples were omitted from specific risk factor long COVID analyses, where sample sizes were too small to contribute, e.g., ALSPAC G0 in the asthma meta-analysis.

Supplementary Note 1: Information governance and ethics for the OpenSAFELY platform

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant;1,2 patient data are pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers who hold contracts with NHS England and only access the platform to initiate database queries and statistical models. Pseudonymised structured data include demographics, medications prescribed from primary care, diagnoses, and laboratory measures. No free text data are included. All database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.3 The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.4 Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic and have been informed of the OpenSAFELY analytics platform. This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (ref 21863).

1 NHS Digital. Data Security and Protection Toolkit. 2020. https://digital.nhs.uk/data-and-information/looking-after-information/data-security-and-information-governance/data-security-and-protection-toolkit (accessed Aug 11, 2020).

2 NHS Digital. BETA - Data Security Standards. 2020. https://digital.nhs.uk/about-nhs-digital/our-work/nhs-digital-data-and-technology-standards/framework/beta---data-security-standards (accessed Aug 11, 2020).

3 NHS Digital. ISB1523: Anonymisation Standard for Publishing Health and Social Care Data. 2020. https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/isb1523-anonymisation-standard-for-publishing-health-and-social-care-data (accessed Aug 11, 2020).

4 Secretary of State for Health-UK Government. Coronavirus (COVID-19): notification to organisations to share information. 2020. https://www.gov.uk/government/publications/coronavirus-covid-19-notification-of-data-controllers-to-share-information (accessed Aug 11, 2020).

Supplementary Note 2: Detail of method to derive long COVID by monthly symptom reporting

Born in Bradford

BiB study members who self-reported COVID-19 were asked to report whether any particular symptoms were present during March-September 2020. Specifically, participants were presented with 27 symptoms (i.e. “decrease in appetite”, “nausea and/or vomiting”, “diarrhoea”, “abdominal pain/tummy ache”, “sore eyes”, “loss of sense of smell or taste”, “sore throat”, “hoarse voice”, “headache”, “dizziness”, “new persistent cough”, “tightness in the chest”, “chest pain”, “shortness of breath”, “fever”, “chills”, “difficulty sleeping”, “felt more tired than normal”, “severe fatigue”, “numbness or tingling somewhere in the body”, “feeling of heaviness in arms or legs”, “achy muscles”, “raised, red, itchy areas on the skin”, “sudden swelling of the face or lips”) and asked to tick whether the symptoms were present for the months March – September 2020. Only 24 of the 27 symptoms were included for consideration as three symptoms (“runny nose”, “sneezing”, and “blocked nose”) were considered non-specific.

They were also asked: (1) whether they had symptoms in the past week (yes; no); (2) whether they think they have had COVID-19 (Yes, confirmed by a positive test; Yes, suspected by a doctor but not tested; Yes, my own suspicions; No) which was re-categorized to a binary response of “yes” if they responded affirmatively and “no” if they did not; (3) if yes to (2), when were you told / when did you think you had COVID-19 (write-in ‘reported positive’ date), and (4) whether they had a positive result from a swab (polymerase chain reaction [PCR]) test (yes; no; don’t know) or an antibody test (yes; no; don’t know) which was re-categorized to a binary variable with “yes” indicating a positive result from a swab or antibody test, “no” indicating a negative result from a swab or antibody test, and those responding “don’t know” coded as missing.

Data were used to derive symptom length categories above by summing included symptoms present for 0-4 weeks; 4-12 weeks or 12+ weeks. Participants were coded to the 0–4-week category if they selected symptoms in the same month as the reported positive date or the participant reported symptoms in the past week and it falls within the same month as positive date (for example, when the reported positive date is after the last symptom month of September and they reported symptoms in the past week).

Participants were coded to the 4–12-week category if they selected 2-3 symptom months. A 3-month duration was allowed only if one of the months is within the same month as the reported positive date.

Participants were coded to the 12+ week category if they selected 3+ symptom months. A 3-month duration was allowed only if the reported positive date was not one of the selected months.

The final analytical sample of long COVID participants (n=110) included only those who responded affirmatively to have had COVID-19 whether confirmed by a positive test, was suspected by doctor but not tested, or from their own judgment.

TwinsUK

In TwinsUK, all study members were asked to report whether they had experienced particular symptoms (33 in total) between February and November 2020. Specifically, twins were presented with 33 symptoms (i.e. “cold or flu symptoms”, “decrease in appetite”, “nausea and/or vomiting”, “diarrhoea”, “abdominal pain/stomach ache”, “runny nose”, “sneezing”, “blocked nose”, “unusual eye soreness or discomfort”, “loss of sense of smell”, “loss of sense of taste”, “sore or painful throat”, “hoarse voice”, “headache”, “dizziness, light-headedness or vertigo”, “shortness of breath or trouble breathing affecting normal activities”, “new persistent cough”, “tightness in the chest”, “chest pain”, “racing heart or palpitations”, “fever”, “chills (feeling too cold)”, “difficulty sleeping”, “felt more tired than normal”, “severe fatigue”, “numbness or tingling somewhere in the body”, “feeling of heaviness in arms or legs”, “strong muscle pains or aches”, “shaking or difficulty while walking”, “phlegm production/chesty cough”, “raised, red, itchy welts on the skin or sudden swelling of the face or lips”, “red/purple sores or blisters on feet”, “confusion, disorientation or drowsiness”) and were asked to report whether they had experienced the listed symptom during the months of February-March 2020; April-May 2020; June-July 2020 (July questionnaire) and / or July-August 2020; September-October 2020 (November questionnaire).

Only 28 of the 33 symptoms were included for consideration as five symptoms (“runny nose”, “sneezing”, “blocked nose”, “shaking or difficulty while walking” and “phlegm production/chesty cough”) were considered non-specific.

Similarly, to BiB, data were used to derive the symptom length categories above through summing whether any of the included symptoms (i.e. were present for 0-4 weeks; 4-12 weeks or 12+ weeks, at any point in time over the specified period. This was performed for people who had had COVID-19 and those who had not (confirmed by negative antibody testing).

Supplementary Note 3: Detail of method to derive inverse probability weights (IPW)

Self-reported COVID-19 status was regressed on each exposure to assess whether COVID-19 was associated with each socio-demographic or pre-pandemic health risk factor. To determine what variables to include across LS, observed associations were meta-analysed to identify consistent predictors of COVID-19 self-report status. To avoid missingness on IPWs, covariates included in each model were imputed using multiple imputation by chained equations (MICE) and IPWs were derived across multiple imputed data sets. All statistical analyses on the LS were performed in Stata version 16 or R (release 3.6.0 or later).

Covariates included in all longitudinal studies

- Sex
- Age
- Ethnicity
- Mental Health Score
- BMI

Additional covariates included in some longitudinal studies

- Asthma (NCDS)
- Smoking (NCDS; BCS70; MCS; NS)

Supplementary References:

1. Brown M, Goodman A, Peters A, Ploubidis GB, Sanchez A, Silverwood R, et al. COVID-19 Survey in Five National Longitudinal Studies: Wave 1, 2 and 3. User Guide (Version 3). UCL Cent Longitud Stud MRC Unit Lifelong Heal Ageing London, UK [Internet]. 2020;(June):1–62. Available from: https://cls.ucl.ac.uk/wp-content/uploads/2021/01/UCL-Cohorts-COVID-19-Survey-user-guide.pdf

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5. Elliott J, Shepherd P. Cohort profile: 1970 British Birth Cohort (BCS70). Int J Epidemiol. 2006;35(4):836–43.

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12. Verdi S, Abbasian G, Bowyer RCE, Lachance G, Yarand D, Christofidou P, et al. TwinsUK: The UK Adult Twin Registry Update. Twin Res Hum Genet. 2019;(May 2007):1–7.

13. Suthahar A, Sharma P, Hart D, García MP, Horsfall R, Bowyer RCE, et al. TwinsUK COVID-19 personal experience questionnaire (CoPE): wave 1 data capture April-May 2020 [version 1 ; peer review : awaiting peer review]. 2021;(May 2020):1–10.