

1 **Supplementary Methods**

2 **UK Biobank**

3 The UK Biobank study was approved by the National Health Service National Research Ethics
4 Service (ref. 11/NW/0382), and all participants provided written informed consent to
5 participate in the UK Biobank study.

6 **Shift Work Assessment**

7 We defined shift work as previously reported by Vetter et al (1), however, we combined
8 'irregular or rotating shifts with some night shifts' and 'irregular or rotating shifts with
9 usual night shifts' to form one group 'irregular shift work including nights'. Briefly,
10 participants employed at baseline were asked to report whether their current main job
11 involved shift work (i.e. a schedule falling outside of 9:00am to 5:00pm; by definition, such
12 schedules involved afternoon, evening or night shifts (or rotating through these shifts)). If
13 yes, participants were further asked whether their main job involved night shifts, defined as
14 '...a work schedule that involves working through the normal sleeping hours, for instance,
15 working through the hours from 12:00am to 6:00am'. For both questions, response options
16 were 'never/rarely', 'sometimes', 'usually', or 'always' and included additional options:
17 'prefer not to answer' and 'do not know'. Based on those two questions, we derived
18 participants' current shift work status, categorized as 'day workers', 'shift worker, but only
19 rarely if ever nights', 'irregular shift work including nights' and 'permanent night shifts'.
20 In the lifetime employment assessment, individuals reported each job ever worked, the
21 number of years in each job ever worked, the number of years in each job, and the number
22 of night shifts per month each job entailed. We restricted our analysis to those individuals

23 who provided in depth lifetime employment information (N= 107,930), we restricted the
24 employment history to only jobs worked prior to 2008, since this was when the diagnosis of
25 asthma was taken at baseline. We aggregated duration (i.e., number of years working night
26 shifts) and frequency (i.e., the average number of night shifts per month) of night shift work.

27 **Asthma Definition**

28 Cases of asthma were defined by including all those participants with doctor diagnosed
29 asthma at baseline as well as also being on any medication used to treat asthma as defined
30 by Shrine et al. 2019 (2). Cases of moderate-severe asthma were defined as having doctor
31 diagnosed asthma at baseline as well as meeting BTS step 3-5 criteria, i.e. for stage 3 taking
32 β 2 agonists plus inhaled corticosteroid; stage 4 taking higher dose inhaled corticosteroids
33 than stage 3 patients and addition of a fourth drug (eg, leukotriene receptor antagonist,
34 theophylline); and stage 5, taking oral corticosteroid or omalizumab, or both (2). We
35 excluded participants with doctor-diagnosed asthma who reported not to be on asthma
36 medication (N=18,806) and those on asthma medication but who did not have doctor
37 diagnosed asthma (N=1,345) from our analyses. When analysing the risk of moderate-severe
38 we further excluded participants with asthma taking medication on BTS stage 1 and 2
39 (N=9,455).

40 Within the parameters from the UK Biobank assessment centre data was the question
41 relating to whether a participant had experienced 'Wheeze or whistling in the chest in the
42 last year'. We excluded participants who answered "Do not know" or "Prefer not to answer"
43 from any statistical analyses. Forced expiratory volume in 1-second (FEV₁), predicted
44 percentage, was also analysed. FEV₁ predicted percentages were calculated (3). FEV₁
45 predicted percentages were filtered to produce two sub-populations; FEV₁ \geq 80% and FEV₁ <

46 80%, with the latter indicative of an obstructive respiratory pathology (4, 5) e.g. asthma (6,
47 7). Participants were split into 'yes' and 'no' sub-populations for 'Wheeze or whistling in the
48 chest in the last year'. These and the FEV₁ predicted percentage sub-populations were
49 further split according to participant's current work shift schedule, previously outlined.

50 **Occupational Asthma**

51 We identified participants who were employed in jobs that might lead to the development
52 of occupational asthma. These jobs included bakers, food processors, forestry workers,
53 chemical workers, plastics and rubber workers, metal workers, welders, textile workers,
54 electrical and electronic production workers, storage workers, farm workers, waiters,
55 cleaners, painters, dental workers and laboratory technicians (8-11). We also identified
56 occupations, in which a medical assessment might select against a person with asthma
57 (Protective Service Officers (officers in armed forces, police officers (inspectors and above)
58 and senior officers in fire, ambulance, prison and related services), science technicians and
59 researchers, probation officers and Transport Associate Professionals (including airline pilots
60 and flight engineers, ship and hovercraft officers, train drivers). Both of these were included
61 as covariates in models 2 and 3.

62 **Chronotype**

63 Participants self-reported chronotype on a touch-screen questionnaire at baseline by
64 answering a question taken from the Morningness-Eveningness questionnaire (question
65 19;[12]). The question asks: "Do you consider yourself to be...." with response options
66 "Definitely a 'morning' person", "More a 'morning' than 'evening' person", "More an
67 'evening' than a 'morning' person," "Definitely an 'evening' person," "Do not know," and

68 “Prefer not to answer.” Subjects who responded “Do not know” or “Prefer not to answer”
69 were set to missing. This single item has been shown to correlate with sleep timing and dim-
70 light melatonin onset (13-15). For our analyses we combined “more a ‘morning’ than
71 ‘evening’ person” with “more an ‘evening’ than ‘morning’ person” to form an intermediate
72 group. In our initial analysis of chronotype in asthma, we included all individuals with
73 asthma and chronotype information, N= 413,040 (N=398,252 for moderate-severe asthma).
74 Subsequently we investigated shift work in asthma stratified by chronotype (N = 228,671);
75 this excluded participants not in paid employment or self-employed at baseline, or
76 answered “Do not know” or “Prefer not to say” when asked (N=169,581).

77 **Genetic Risk Score for Asthma**

78 Genotyping in the UK Biobank was performed on two arrays, UK BiLEVE and UK Biobank
79 Azim. Genotyping, quality control, and imputation procedures have been previously
80 described (16). A total of 488,232 participants in the UK Biobank were genotyped. In total,
81 337,409 unrelated samples of European ancestry were then filtered and those with an
82 incomplete diagnosis of asthma were excluded, leaving 313,816 for analysis (302,686 for
83 moderate/severe asthma).

84 We derived a genetic risk score (GRS) for asthma and moderate/severe asthma using 24
85 GWAS SNPs previously reported by Shrine et al. 2019 (2) for each individual participant. The
86 GRS was generated using PLINK by summing the number of risk (asthma-increasing) alleles,
87 which were weighted by the respective allelic effect size (β -coefficient) from the discovery
88 GWAS. For variants not available in UK Biobank, we used the corresponding proxy SNP as
89 indicated in Table 2 within (2). Scaling of the individual GRS was performed to allow
90 interpretation of the effects as a per-1 risk allele increase in the GRS (division by twice the

91 sum of the β -coefficients and multiplication by twice the square of the SNP count
92 representing the maximum number of risk alleles). Analysis of GRS was performed by
93 subdividing into quartiles, as well as the impact per-1 risk allele. Analysis of the shift work
94 effect on asthma was performed on all GRS quartiles. The interaction between GRS quartiles
95 and shift work schedule was tested and a P value for interaction was computed.

96 When investigating continuous variables (lifetime duration and frequency of shift work
97 including nights (**Figure 3**), and odds by genetic risk score (**Supplementary Tables 6 and 7**) p-
98 values for the linear trend were obtained by considering the variable as continuous and
99 running a Wald test to calculate the significance of the variable in our models.

100 To analyse the effect of GRS and chronotype on the relationship of current job shift
101 schedule on asthma risk we compared models with and without an interaction term
102 (between job shift schedule and GRS/chronotype). The two models were compared using a
103 likelihood ratio test and a p-value indicating the significance of the interaction computed.

104 **Supplemental References**

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Supplementary Figure 1: STROBE diagram showing filtering of participants for each analysis. STROBE diagram showing how the full UK Biobank cohort (N=502,540) was filtered for each analysis. Blue boxes correspond to individuals used for the analyses resulting in each figure/table. White boxes show excluded participants at each stage.

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Supplementary Table 1: Job Standard Occupational Classification (SOC) category splits by current night shift work exposure (N = 76,162)

	Current work schedule			
	Day workers	Shift work, but never or rarely night shifts	Irregular shift work including nights	Permanent night shift work
N	66360	4986	3640	1176
Time in most recent job (years)	20.46 (13.01)	20.25 (13.41)	21.62 (13.26)	23.77 (13.34)
Managers and Senior Officials (%)	17.49	12.8	9.59	6.21
Professional Occupations (%)	36.29	18.47	14.67	5.7
Associate Professional and Technical Occupations (%)	18.25	29.1	39.67	38.27
Administrative and Secretarial Occupations (%)	14.27	9.73	4.48	6.55
Skilled Trades Occupations (%)	4.12	6.28	8.74	7.4
Personal Service Occupations (%)	3.64	7.82	8.05	10.03
Sales and Customer Service Occupations (%)	2.39	4.83	2.01	1.87
Process, Plant and Machine Operatives (%)	1.54	6.14	9.09	13.69
Elementary Occupations (%)	2.03	4.83	3.71	10.29

166 are mean (SD) or percentages.

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Supplementary Table 2: Adjusted odds (95% CI) of any asthma by current shift work exposure
(N=266,674)

	Current work schedule			
	Day workers	Shift work, but never or rarely night shifts	Irregular shift work including nights	Permanent night shift work
Total cases (% of total sample size)	11,695 (5.31%)	1,306 (5.72%)	872 (5.15%)	365 (5.48%)
Total sample size	220,234	22,838	16,945	6,657
Model 1: Age and Sex adjusted OR (95% CI)	1 (referent)	1.08 (1.02-1.15)	0.98 (0.91-1.05)	1.05 (0.95-1.17)
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.06 (0.95-1.18)	1.08 (0.95-1.22)	1.23 (1.03-1.46)
Model 3: Model 2 covariates + Sleep Duration (95% CI)	1 (referent)	1.06 (0.95-1.18)	1.07 (0.94-1.21)	1.20 (1.01-1.43)

Model 2 covariates: age, sex, smoking status, smoking pack years, alcohol status, daily alcohol intake, ethnicity, Townsend deprivation index, days exercised (walked, moderate and vigorous), BMI, chronotype, length of working week, job asthma risk and job medical required. Model 3 are adjusted for Model 2 covariates plus sleep duration.

196 Supplementary Table 3: Adjusted odds (95% CI) of moderate-severe asthma by
 197 chronotype (N = 398,252)

	Chronotype		
	Intermediate chronotype	Definitely a morning person	Definitely an evening person
Total cases (% of total sample size)	5,820 (2.28%)	2,782 (2.58%)	1,002 (2.85%)
Total sample size	255,089	108,003	35,160
Model 1: Age and Sex adjusted OR (95% CI)	1 (referent)	1.10 (1.06-1.16)	1.30 (1.21-1.39)
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.19 (1.05-1.36)	1.18 (0.99-1.39)
Model 3: Model 2 covariates + Sleep Duration (95% CI)	1 (referent)	1.19 (1.05-1.35)	1.17 (0.99-1.38)

198 Model 2 covariates: age, sex, smoking status, smoking pack years, alcohol status, daily
 199 alcohol intake, ethnicity, Townsend deprivation index, days exercised (walked,
 200 moderate and vigorous), BMI, length of working week, job asthma risk and job medical
 201 required. Model 3 data are adjusted for Model 2 covariates plus sleep duration.
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203 Supplementary Table 4: Adjusted odds (95% CI) and association of moderate-
 204 severe asthma and current shift work exposure by chronotype

Current work schedule	OR (95% CI)	P _{interaction}
Definite morning chronotype (N= 59,621, 1,216 cases)		
Day workers	1 (referent)	0.21
Shift work, but never or rarely night shifts	0.97 (0.67-1.39)	
Irregular shift work including nights	1.55 (1.06-2.27)	
Permanent night shift work	1.32 (0.69-2.51)	
Intermediate chronotype (N= 148,216, 2,645 cases)		
Day workers	1 (referent)	
Shift work, but never or rarely night shifts	1.13 (0.90-1.43)	
Irregular shift work including nights	1.11 (0.84-1.47)	
Permanent night shift work	1.33 (0.88-2.00)	
Definite evening chronotype (N= 20,834, 447 cases)		
Day workers	1 (referent)	
Shift work, but never or rarely night shifts	1.18 (0.70-1.99)	
Irregular shift work including nights	1.10 (0.61-1.99)	
Permanent night shift work	1.52 (0.88-2.65)	

205 Models were adjusted for covariates in model 2 (age, sex, smoking status,
 206 smoking pack years, alcohol status, daily alcohol intake, ethnicity, Townsend
 207 deprivation index, days exercised (walked, moderate and vigorous), BMI, length
 208 of working week, job asthma risk and job medical required).
 209 Interaction p-value is calculated using a LR test comparing the model with and
 210 without an interaction term.
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Supplementary Table 5: Adjusted odds (95% CI) of moderate-severe asthma by genetic risk score (GRS) quartile (N = 302,686)

	GRS quartile				p-value for trend
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Total cases (% of total sample size)	1,166 (1.50%)	1,585 (2.07%)	1,906 (2.53%)	2,707 (3.71%)	
Total sample size	77,746	76,580	75,435	72,925	
Model 1: Age and Sex adjusted OR (95% CI)	1 (referent)	1.39 (1.29-1.50)	1.70 (1.58-1.83)	2.53 (2.36-2.71)	<0.01
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.22 (0.99-1.52)	1.70 (1.39-2.08)	2.66 (2.21-3.22)	<0.01
Model 3: Model 2 covariates + Sleep Duration (95% CI)	1 (referent)	1.23 (0.99-1.52)	1.71 (1.40-2.09)	2.67 (2.21-3.23)	<0.01

Model 2 covariates: age, sex, smoking status, smoking pack years, alcohol status, daily alcohol intake, Townsend deprivation index, days exercised (walked, moderate and vigorous), BMI, phenotype, length of working week, job asthma risk and job medical required. Model 3 data are adjusted for Model 2 covariates plus sleep duration.

Supplementary Table 6: Adjusted odds (95% CI) of any asthma by genetic risk score (GRS) quartile (N = 313,816)

	GRS quartile				p-value for trend
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Total cases (% of total sample size)	3,106 (3.90%)	3,942 (4.99%)	4,818 (6.15%)	6,628 (8.63%)	
Total sample size	79,686	78,937	78,347	76,846	
Model 1: Age and Sex adjusted OR	1 (referent)	1.30 (1.23-1.36)	1.62 (1.54-1.69)	2.33 (2.23-2.43)	<0.01
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.24 (1.09-1.41)	1.52 (1.35-1.72)	2.33 (2.08-2.61)	<0.01
Model 3: Model 2 covariates + Sleep Duration (95% CI)	1 (referent)	1.24 (1.10-1.41)	1.53 (1.35-1.72)	2.33 (2.08-2.61)	<0.01

Model 2 covariates: age, sex, smoking status, smoking pack years, alcohol status, daily alcohol intake, Townsend deprivation index, days exercised (walked, moderate and vigorous), BMI, ethnicity, length of working week, job asthma risk and job medical required. Model 3 data are adjusted for Model 2 covariates plus sleep duration.

226 Supplementary Table 7: Adjusted odds (95% CI) and association of moderate-
 227 severe asthma and current shift work exposure by genetic risk

Current work schedule	OR (95% CI)	P _{interaction}
GRS first quartile (lowest) (N= 44,088, 475 cases)		
Day workers	1 (referent)	<0.05
Shift work, but never or rarely night shifts	1.18 (0.71-1.96)	
Irregular shift work including nights	0.74 (0.35-1.53)	
Permanent night shift work	1.67 (0.80-3.51)	
GRS second quartile (N= 43,396, 667 cases)		
Day workers	1 (referent)	
Shift work, but never or rarely night shifts	1.78 (1.17-2.68)	
Irregular shift work including nights	1.26 (0.72-2.23)	
Permanent night shift work	1.57 (0.75-3.27)	
GRS third quartile (N= 42,507, 846 cases)		
Day workers	1 (referent)	
Shift work, but never or rarely night shifts	1.41 (0.95-2.09)	
Irregular shift work including nights	1.22 (0.74-2.02)	
Permanent night shift work	2.04 (1.11-3.74)	
GRS fourth quartile (highest) (N= 40,905, 1,218 cases)		
Day workers	1 (referent)	
Shift work, but never or rarely night shifts	0.93 (0.64-1.35)	
Irregular shift work including nights	1.42 (0.97-2.10)	
Permanent night shift work	1.52 (0.90-2.56)	

228 Models were adjusted for covariates in model 2 (age, sex, smoking status,
 229 smoking pack years, alcohol status, daily alcohol intake, ethnicity, Townsend
 230 deprivation index, days exercised (walked, moderate and vigorous), BMI,
 231 chronotype, length of working week, job asthma risk and job medical required).
 232 Interaction p-value is calculated using a LR test comparing the model with and
 233 without an interaction term.

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Supplementary Table 8: Adjusted odds (95% CI) of moderate-severe asthma by current shift work exposure after excluding participants with doctor diagnosed Chronic Obstructive Pulmonary Disease (COPD), emphysema or chronic bronchitis (N = 255,647)

	Current work schedule			
	Day workers	Shift work, but never or rarely night shifts	Irregular shift work including nights	Permanent night shift work
Total cases (% of total sample size)	3,668 (1.74%)	418 (1.92%)	267 (1.65%)	119 (1.87%)
Total sample size	211,283	21,787	16,225	6,352
Model 1: Age and Sex adjusted OR (95% CI)	1 (referent)	1.12 (1.01-1.24)	1.02 (0.90-1.15)	1.15 (0.96-1.39)
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.15 (0.96-1.39)	1.13 (0.90-1.40)	1.35 (1.01-1.82)
Model 3: Model 2 covariates + Sleep Duration (95% CI)	1 (referent)	1.15 (0.96-1.38)	1.12 (0.90-1.39)	1.33 (0.99-1.79)

Model 2 covariates: age, sex, smoking status, smoking pack years, alcohol status, daily alcohol intake, ethnicity, Townsend deprivation index, days exercised (walked, moderate and vigorous), BMI, chronotype, length of working week, job asthma risk and job medical required. Model 3 are adjusted for Model 2 covariates plus sleep duration.

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Supplementary Table 9: Adjusted odds (95% CI) of any asthma by current shift work exposure after excluding participants with doctor diagnosed Chronic Obstructive Pulmonary Disease (COPD), emphysema or chronic bronchitis (N = 264,884)

	Current work schedule			
	Day workers	Shift work, but never or rarely night shifts	Irregular shift work including nights	Permanent night shift work
Total cases (% of total sample size)	11,290 (5.16%)	1,247 (5.51%)	823 (4.90%)	349 (5.30%)
Total sample size	218,905	22,616	16,781	6,582
Model 1: Age and Sex adjusted OR (95% CI)	1 (referent)	1.07 (1.01-1.14)	0.96 (0.89-1.03)	1.04 (0.93-1.16)
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.04 (0.93-1.16)	1.05 (0.92-1.19)	1.26 (1.05-1.50)
Model 3: Model 2 covariates + Sleep Duration (95% CI)	1 (referent)	1.04 (0.93-1.16)	1.04 (0.91-1.18)	1.23 (1.03-1.48)

Model 2 covariates: age, sex, smoking status, smoking pack years, alcohol status, daily alcohol intake, ethnicity, Townsend deprivation index, days exercised (walked, moderate and vigorous), BMI, chronotype, length of working week, job asthma risk and job medical required. Model 3 are adjusted for Model 2 covariates plus sleep duration.

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