

Supplementary Table 1. Concordance of smoking status as per latest UK Biobank record and latest TPP record, brackets in cells correspond to the row percentage (n=109,641 with smoking data recorded in both datasets). Median time between latest record and study period was 4.5 years (IQR: 0.9-13.1 years).

| Biobank smoking data | TPP smoking data | | | | |
|----------------------|-------------------|-------------------|----------------|-----------------|----------------|
| | Never-smoker | Ex-smoker | Light smoker | Moderate smoker | Heavy smoker |
| Never-smoker | 34,645 (75.96) | 10,898 (23.90) | 39 (0.09) | 17 (0.04) | <10 |
| Ex-smoker | 3,170 (5.77) | 51,547 (93.89) | 97 (0.18) | 58 (0.11) | 28 (0.05) |
| Light smoker | 68 (3.42) | 1,549 (77.96) | 282 (14.19) | 80 (4.03) | <10 |
| Moderate smoker | 86 (2.10) | 3,038 (74.15) | 304 (7.42) | 562 (13.72) | 107 (2.61) |
| Heavy smoker | 60 (1.97) | 2,110 (69.18) | 112 (3.67) | 372 (12.20) | 396 (12.98) |

Supplementary Table 2. Concordance of smoking status as per latest UK Biobank record and latest EMIS record, brackets in cells correspond to the row percentage (n=229,583 with smoking data recorded in both datasets). Median time between latest record and study period was 1.1 years (IQR: 0.4-3.4 years).

| Biobank smoking data | EMIS smoking data | | | | |
|-----------------------------|--------------------------|-------------------|----------------|-----------------|----------------|
| | Never-smoker | Ex-smoker | Light smoker | Moderate smoker | Heavy smoker |
| Never-smoker | 129,776 (97.21) | 3,705 (2.78) | 14 (0.01) | <10 (0.01) | <10 (<0.01) |
| Ex-smoker | 21,941 (26.56) | 60,309 (72.99) | 164 (0.20) | 124 (0.15) | 84 (0.10) |
| Light smoker | 258 (8.42) | 2,083 (68.01) | 573 (18.71) | 141 (4.60) | <10 (0.26) |
| Moderate smoker | 349 (5.97) | 3,762 (64.32) | 580 (9.92) | 997 (17.05) | 161 (2.75) |
| Heavy smoker | 202 (4.45) | 2,791 (61.44) | 200 (4.40) | 707 (15.56) | 643 (14.15) |

Supplementary Table 3. Output of maximally adjusted sample selection logistic regression model (likelihood to receive a SARS-CoV-2 test), which was used to generate inverse probability weights for the maximally adjusted observational analysis model for effect of smoking on confirmed infection.

| Parameter | (tested / not tested) | Odds ratio (95% confidence interval) |
|---------------------------------------|-----------------------|--------------------------------------|
| <i>Smoking status</i> | | |
| Never smoker (reference) | (6,565/226,930) | 1 |
| Former smoker | (5,135/139,482) | 1.16 (1.12 to 1.20) |
| Light smoker | (200/5,745) | 1.14 (0.96 to 1.35) |
| Moderate smoker | (471/11,421) | 1.35 (1.19 to 1.55) |
| Heavy smoker | (457/8,977) | 1.54 (1.32 to 1.79) |
| <i>Sex</i> | | |
| Female (reference) | (6,841/224,115) | 1 |
| Male | (6,457/180,349) | 1.06 (1.02 to 1.10) |
| <i>Age category</i> | | |
| 40 – 49 years | (33/1,160) | 0.96 (0.68 to 1.37) |
| 50 – 59 years (reference) | (2,644/93,494) | 1 |
| 60 – 69 years | (1,625/135,812) | 0.92 (0.88 to 0.97) |
| 70 – 79 years | (6,527/166,822) | 1.29 (1.23 to 1.35) |
| 80 + years | (469/7,176) | 2.09 (1.89 to 2.31) |
| <i>Ethnicity</i> | | |
| White (reference) | (12,274/378,752) | 1 |
| Mixed race | (91/2,510) | 1.12 (0.90 to 1.38) |
| Asian or Asian British | (273/7,083) | 1.10 (0.97 to 1.24) |
| Chinese | (34/1,375) | 0.85 (0.60 to 1.20) |
| Other Asian | (53/1,600) | 0.95 (0.72 to 1.25) |
| Black or Black British | (325/7,175) | 1.29 (1.15 to 1.45) |
| Other | (168/2,041) | 1.24 (1.06 to 1.45) |
| <i>Townsend deprivation quintile</i> | | |
| 1 (reference) | (5,543/186,697) | 1 |
| 2 | (2,740/90,549) | 1.0 (0.96 to 1.06) |
| 3 | (2,021/58,677) | 1.13 (1.07 to 1.19) |
| 4 | (1,963/47,637) | 1.31 (1.24 to 1.39) |
| 5 (least affluent) | (1,031/20,904) | 1.48 (1.38 to 1.59) |
| <i>Comorbidities</i> | | |
| Bronchiectasis | (45/499) | 1.75 (1.27 to 2.40) |
| Chronic liver disease | (100/1,096) | 2.22 (1.80 to 2.74) |
| Cystic fibrosis | (<10 / <10) | 3.61 (0.39 to 33.5) |
| Diabetes mellitus | (1,262/20,392) | 1.58 (1.47 to 1.67) |
| Interstitial lung disease | (30/251) | 2.54 (1.73 to 3.75) |
| Asthma | (154/2,212) | 1.65 (1.39 to 1.95) |
| Atrial fibrillation | (525/7,555) | 1.62 (1.48 to 1.78) |
| Chronic obstructive pulmonary disease | (291/3,048) | 1.96 (1.72 to 2.22) |
| Chronic kidney disease | | <i>Not estimable</i> |
| Stage 2 | | |
| Stage 3 | (<10/21) | 4.61 (1.66 to 12.79) |
| Stage 4 | (<10/18) | 5.09 (1.63 to 15.92) |
| Stage 5 / End-stage renal failure | (48/197) | 5.54 (3.99 to 7.69) |
| Unspecified | (58/343) | 3.71 (2.78 to 4.94) |
| Congestive cardiac failure | (151/1,166) | 1.92 (1.60 to 2.29) |
| Hypertension | (75/1,115) | 1.54 (1.21 to 1.96) |
| Ischaemic heart disease | (1,463/23,197) | 1.54 (1.45 to 1.64) |
| Lung cancer | (61/634) | 2.04 (1.57 to 2.69) |

Supplementary Table 4. Results from multivariable logistic regression models examining effect of smoking on outcomes of interest with serial adjustment guided by directed acyclic graphs. CI = confidence interval, COVID-19 = novel coronavirus disease 2019, BMI = body mass index, A = interstitial lung disease, cystic fibrosis, bronchiectasis, chronic liver disease, diabetes (type 1 or 2), B = lung cancer, asthma, chronic obstructive pulmonary disease, hypertension, ischaemic heart disease, congestive cardiac failure, chronic kidney disease, atrial fibrillation.

| Smoking category | (cases / controls) | Odds ratio (95% CI) adjusted for age and sex | Odds ratio (95% CI) adjusting for age, sex, ethnicity, deprivation and non-smoking related comorbidity ^A | Odds ratio (95% CI) adjusting for age, sex, ethnicity, deprivation, non- smoking related comorbidity ^A , smoking-related comorbidity ^B and BMI |
|---|--------------------|---|---|---|
| <i>Confirmed SARS-CoV-2 infection (1,649 / 419,444)</i> | | | | |
| Never smoker | 849 / 251,126 | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | 717 / 154,708 | 1.34 (1.21 to 1.48) | 1.31 (1.19 to 1.45) | 1.26 (1.13 to 1.40) |
| Light smoker (1-9/day) | 18 / 3,923 | 1.28 (0.80 to 2.04) | 1.09 (0.68 to 1.74) | 1.09 (0.67 to 1.77) |
| Moderate smoker (10-19/day) | 26 / 5,753 | 1.27 (0.86 to 1.88) | 1.12 (0.75 to 1.65) | 1.13 (0.76 to 1.69) |
| Heavy smoker (20+/day) | 13 / 3,934 | 0.90 (0.52 to 1.56) | 0.79 (0.46 to 1.38) | 0.75 (0.42 to 1.33) |
| Never smoker | 849 / 251,126 | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | 717 / 154,708 | 1.34 (1.21 to 1.48) | 1.31 (1.19 to 1.45) | 1.26 (1.13 to 1.40) |
| Current smoker | 57 / 13,610 | 1.16 (0.89 to 1.52) | 1.01 (0.77 to 1.33) | 1.00 (0.76 to 1.32) |
| <i>Confirmed SARS-CoV-2 infection (weighted by inverse probability of receiving a test)</i> | | | | |
| Never smoker | 849 / 251,126 | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | 717 / 154,708 | 1.07 (0.97 to 1.19) | 1.10 (0.98 to 1.22) | 1.12 (1.00 to 1.25) |
| Light smoker (1-9/day) | 18 / 3,923 | 1.01 (0.63 to 1.64) | 1.09 (0.66 to 1.79) | 1.11 (0.67 to 1.83) |
| Moderate smoker (10-19/day) | 26 / 5,753 | 0.82 (0.55 to 1.23) | 0.81 (0.54 to 1.23) | 0.86 (0.57 to 1.30) |
| Heavy smoker (20+/day) | 13 / 3,934 | 0.50 (0.29 to 0.89) | 0.54 (0.30 to 0.97) | 0.55 (0.31 to 0.99) |
| Never smoker | 849 / 251,126 | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | 717 / 154,708 | 1.07 (0.97 to 1.19) | 1.10 (0.98 to 1.22) | 1.12 (1.00 to 1.24) |
| Current smoker | 57 / 13,610 | 0.76 (0.57 to 1.00) | 0.78 (0.59 to 1.04) | 0.82 (0.61 to 1.09) |

| <i>Hospitalisation related to COVID-19 (968 / 419,444)</i> | | | | | | | |
|--|---------------|------|-----------------|------|-----------------|------|-----------------|
| Never smoker | 440 / 251,126 | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | 457 / 154,708 | 1.44 | (1.26 to 1.64) | 1.40 | (1.22 to 1.60) | 1.31 | (1.14 to 1.50) |
| Light smoker (1-9/day) | 12 / 3,923 | 1.82 | (1.03 to 3.24) | 1.43 | (0.80 to 2.54) | 1.31 | (0.69 to 2.46) |
| Moderate smoker (10-19/day) | 25 / 5,753 | 2.59 | (1.72 to 3.87) | 2.13 | (1.41 to 3.19) | 2.26 | (1.50 to 3.41) |
| Heavy smoker (20+/day) | 14 / 3,934 | 1.97 | (1.16 to 3.37) | 1.64 | (0.96 to 2.80) | 1.65 | (0.96 to 2.84) |
| Never smoker | 440 / 251,126 | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | 457 / 154,708 | 1.44 | (1.26 to 1.64) | 1.40 | (1.22 to 1.60) | 1.31 | (1.14 to 1.50) |
| Current smoker | 51 / 13,610 | 2.19 | (1.63 to 2.92) | 1.78 | (1.32 to 2.39) | 1.80 | (1.26 to 2.29) |
| <i>Death related to COVID-19 (444 / 419,444)</i> | | | | | | | |
| Never smoker | 159 / 251,126 | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | 223 / 154,708 | 1.76 | (1.43 to 2.16) | 1.67 | (1.36 to 2.06) | 1.60 | (1.29 to 1.99) |
| Light smoker (1-9/day) | <10 / 3,923 | 3.35 | (1.57 to 7.16) | 2.72 | (1.27 to 5.82) | 2.14 | (0.87 to 5.24) |
| Moderate smoker (10-19/day) | 20 / 5,753 | 6.65 | (4.17 to 10.62) | 5.54 | (3.45 to 8.89) | 5.91 | (3.66 to 9.54) |
| Heavy smoker (20+/day) | 16 / 3,934 | 7.44 | (4.42 to 12.49) | 6.09 | (3.60 to 10.31) | 6.11 | (3.59 to 10.42) |
| Never smoker | 159 / 251,126 | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | 223 / 154,708 | 1.76 | (1.43 to 2.16) | 1.67 | (1.36 to 2.06) | 1.60 | (1.29 to 1.97) |
| Current smoker | 43 / 13,610 | 5.93 | (4.22 to 8.33) | 4.87 | (3.44 to 6.88) | 4.89 | (3.41 to 7.00) |

Supplementary Table 5. Results from models using smoking status derived from UK Biobank data only. The latest of UK Biobank follow-up assessment and baseline assessment were used. This sensitivity analysis was used to ascertain the possible impact of reverse causation on our results. Compared to using the most recent smoking status available, the results using UK Biobank data only (measured at median 10.6 years prior to 1st Jan 2020) preserved the direction of the risks, but with odds ratios of lower magnitude.

CI = confidence interval, COVID-19 = novel coronavirus disease 2019, BMI = body mass index, A = interstitial lung disease, cystic fibrosis, bronchiectasis, chronic liver disease, diabetes (type 1 or 2), B = lung cancer, asthma, chronic obstructive pulmonary disease, hypertension, ischaemic heart disease, congestive cardiac failure, chronic kidney disease, atrial fibrillation.

| Smoking category | (cases/controls) | Odds ratio (95% CI) adjusted for age and sex | Odds ratio (95% CI) adjusting for demographics and non- smoking related comorbidity ^A | Odds ratio (95% CI) adjusting for demographics, non- smoking related comorbidity ^A , smoking- related comorbidity ^B and BMI |
|--|------------------|---|--|--|
| <i>Confirmed SARS-CoV-2 infection</i> | | (1,567/403,934) | | |
| Never smoker | (806/232,822) | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | (645/143,976) | 1.28 (1.15 to 1.43) | 1.28 (1.15 to 1.43) | 1.24 (1.11 to 1.39) |
| Light smoker (1-9/day) | (23/5,926) | 1.09 (0.72 to 1.66) | 0.97 (0.64 to 1.47) | 0.99 (0.65 to 1.52) |
| Moderate smoker (10-19/day) | (53/11,829) | 1.27 (0.96 to 1.67) | 1.12 (0.85 to 1.49) | 1.13 (0.85 to 1.50) |
| Heavy smoker (20+/day) | (40/9,381) | 1.17 (0.85 to 1.61) | 1.03 (0.75 to 1.42) | 0.98 (0.71 to 1.37) |
| Never smoker | (806/232,822) | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | (645/143,976) | 1.28 (1.15 to 1.43) | 1.28 (1.15 to 1.43) | 1.24 (1.11 to 1.39) |
| Current smoker | (116/27,136) | 1.19 (0.98 to 1.45) | 1.06 (0.87 to 1.29) | 1.04 (0.85 to 1.28) |
| <i>Hospitalisation related to COVID-19</i> | | (909/403,934) | | |
| Never smoker | (420/232,822) | 1 (reference) | 1 (reference) | 1 (reference) |
| Former smoker | (402/143,976) | 1.33 (1.16 to 1.53) | 1.32 (1.15 to 1.52) | 1.22 (1.05 to 1.41) |
| Light smoker (1-9/day) | (14/5,926) | 1.44 (0.84 to 2.45) | 1.21 (0.71 to 2.07) | 1.24 (0.71 to 2.17) |
| Moderate smoker (10-19/day) | (35/11,829) | 1.72 (1.21 to 2.42) | 1.44 (1.01 to 2.04) | 1.47 (1.03 to 2.08) |

| | | | | | | | |
|----------------------------------|---------------|---------------|----------------|------|----------------|------|----------------|
| Heavy smoker (20+/day) | (38/9,381) | 2.20 | (1.57 to 3.07) | 1.83 | (1.30 to 2.57) | 1.79 | (1.27 to 2.52) |
| Never smoker | (420/232,822) | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | (402/143,976) | 1.33 | (1.16 to 1.53) | 1.32 | (1.15 to 1.52) | 1.22 | (1.05 to 1.41) |
| Current smoker | (87/27,136) | 1.83 | (1.45 to 2.31) | 1.53 | (1.21 to 1.94) | 1.54 | (1.22 to 1.96) |
| <i>Death related to COVID-19</i> | | (419/403,934) | | | | | |
| Never smoker | (166/232,822) | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | (206/143,976) | 1.53 | (1.25 to 1.89) | 1.49 | (1.20 to 1.83) | 1.41 | (1.14 to 1.74) |
| Light smoker (1-9/day) | (<10/5,926) | 2.04 | (0.96 to 4.35) | 1.76 | (0.82 to 3.76) | 1.38 | (0.57 to 3.38) |
| Moderate smoker (10-19/day) | (22/11,829) | 3.01 | (1.93 to 4.71) | 2.47 | (1.58 to 3.88) | 2.52 | (1.60 to 3.97) |
| Heavy smoker (20+/day) | (18/9,381) | 2.97 | (1.82 to 4.83) | 2.36 | (1.43 to 3.86) | 2.33 | (1.41 to 3.86) |
| Never smoker | (166/232,822) | 1 | (reference) | 1 | (reference) | 1 | (reference) |
| Former smoker | (206/143,976) | 1.53 | (1.25 to 1.89) | 1.49 | (1.20 to 1.83) | 1.41 | (1.14 to 1.74) |
| Current smoker | (47/27,136) | 2.79 | (2.02 to 3.87) | 2.29 | (1.64 to 3.12) | 2.23 | (1.58 to 3.15) |

Supplementary Table 6. Two-sample Mendelian randomisation results for the effects of smoking behaviours on COVID-19 susceptibility and severity (281,105 White British participants)

| Exposure | Outcome | MR method | OR (95% CI) | P-value |
|---------------------------------|---------------------|-------------------|---------------------|----------------|
| Smoking initiation | Confirmed infection | IVW | 1.45 (1.10-1.91) | 0.01 |
| | | MR-Egger | 1.30 (0.41-4.08) | 0.66 |
| | | Weighted median | 1.53 (1.02-2.28) | 0.04 |
| | | MR-PRESSO | 1.45 (1.10-1.91) | 0.01 |
| | Hospitalisation | IVW | 1.60 (1.13-2.27) | 0.01 |
| | | MR-Egger | 1.69 (0.40-7.26) | 0.48 |
| | | Weighted median | 1.62 (0.96-2.72) | 0.07 |
| | | MR-PRESSO | 1.60 (1.14-2.26) | 0.01 |
| | Death | IVW | 1.35 (0.82-2.22) | 0.23 |
| | | MR-Egger | 0.35 (0.04-2.82) | 0.33 |
| | | Weighted median | 1.54 (0.73-3.23) | 0.25 |
| | | MR-PRESSO | 1.35 (0.82-2.22) | 0.23 |
| Smoking heaviness (Ever smoked) | Confirmed infection | IVW | 2.51 (1.20-5.24) | 0.01 |
| | | MR-Egger | 3.40 (0.90-12.87) | 0.07 |
| | | Weighted median | 4.25 (1.33-13.57) | 0.01 |
| | | MR-PRESSO | 2.51 (1.28-4.89) | 0.01 |
| | Hospitalisation | IVW | 5.09 (2.04-12.67) | <.001 |
| | | MR-Egger | 7.14 (1.37-37.14) | 0.02 |
| | | Weighted median | 6.57 (1.54-28.06) | 0.01 |
| | | MR-PRESSO | 5.09 (2.29-11.31) | <.001 |
| | Death | IVW | 10.02 (2.53-39.73) | 0.001 |
| | | MR-Egger estimate | 17.68 (1.42-219.98) | 0.03 |
| | | Weighted median | 21.68 (2.77-169.42) | 0.003 |
| | | MR-PRESSO | 10.02 (2.53-39.73) | 0.002 |

Supplementary Table 7. Tests of heterogeneity, directional pleiotropy, directionality, and regression dilution statistics (n = 281,105)

| Exposure | Outcome | Method | Estimate | P-value |
|---------------------------------|---------------------|-----------------------------|-----------------|----------------|
| Smoking initiation | Confirmed infection | Q statistic | 398.10 | 0.22 |
| | | Egger intercept | 0.00 | 0.84 |
| | | Rucker's Q difference | 0.04 | 0.84 |
| | | MR-PRESSO global test | -- | 0.24 |
| | | Steiger directionality test | -- | <.001 |
| | | I^2_{GX} | 0.98 | |
| | Hospitalisation | Q statistic | 369.51 | 0.60 |
| | | Egger intercept | -0.00 | 0.94 |
| | | Rucker's Q difference | 0.01 | 0.94 |
| | | MR-PRESSO global test | -- | 0.62 |
| | | Steiger directionality test | -- | <.001 |
| | | I^2_{GX} | 0.98 | |
| | Death | Q statistic | 376.28 | 0.50 |
| | | Egger intercept | 0.03 | 0.19 |
| | | Rucker's Q difference | 1.70 | 0.19 |
| | | MR-PRESSO global test | -- | 0.51 |
| | | Steiger directionality test | -- | <.001 |
| | | I^2_{GX} | 0.98 | |
| Smoking heaviness (Ever smoked) | Confirmed infection | Q statistic | 44.35 | 0.82 |
| | | Egger intercept | -0.01 | 0.59 |
| | | Rucker's Q difference | 0.29 | 0.59 |
| | | MR-PRESSO global test | -- | 0.79 |
| | | Steiger directionality test | -- | <.001 |
| | | I^2_{GX} | 0.99 | |
| | Hospitalisation | Q statistic | 41.35 | 0.90 |
| | | Egger intercept | -0.01 | 0.63 |
| | | Rucker's Q difference | 0.23 | 0.63 |
| | | MR-PRESSO global test | -- | 0.88 |
| | | Steiger directionality test | -- | <.001 |
| | | I^2_{GX} | 0.99 | |
| | Death | Q statistic | 66.28 | 0.12 |
| | | Egger intercept | -0.02 | 0.60 |
| | | Rucker's Q difference | 0.35 | 0.56 |
| | | MR-PRESSO global test | -- | 0.12 |
| | | Steiger directionality test | -- | <.001 |
| | | I^2_{GX} | 0.99 | |

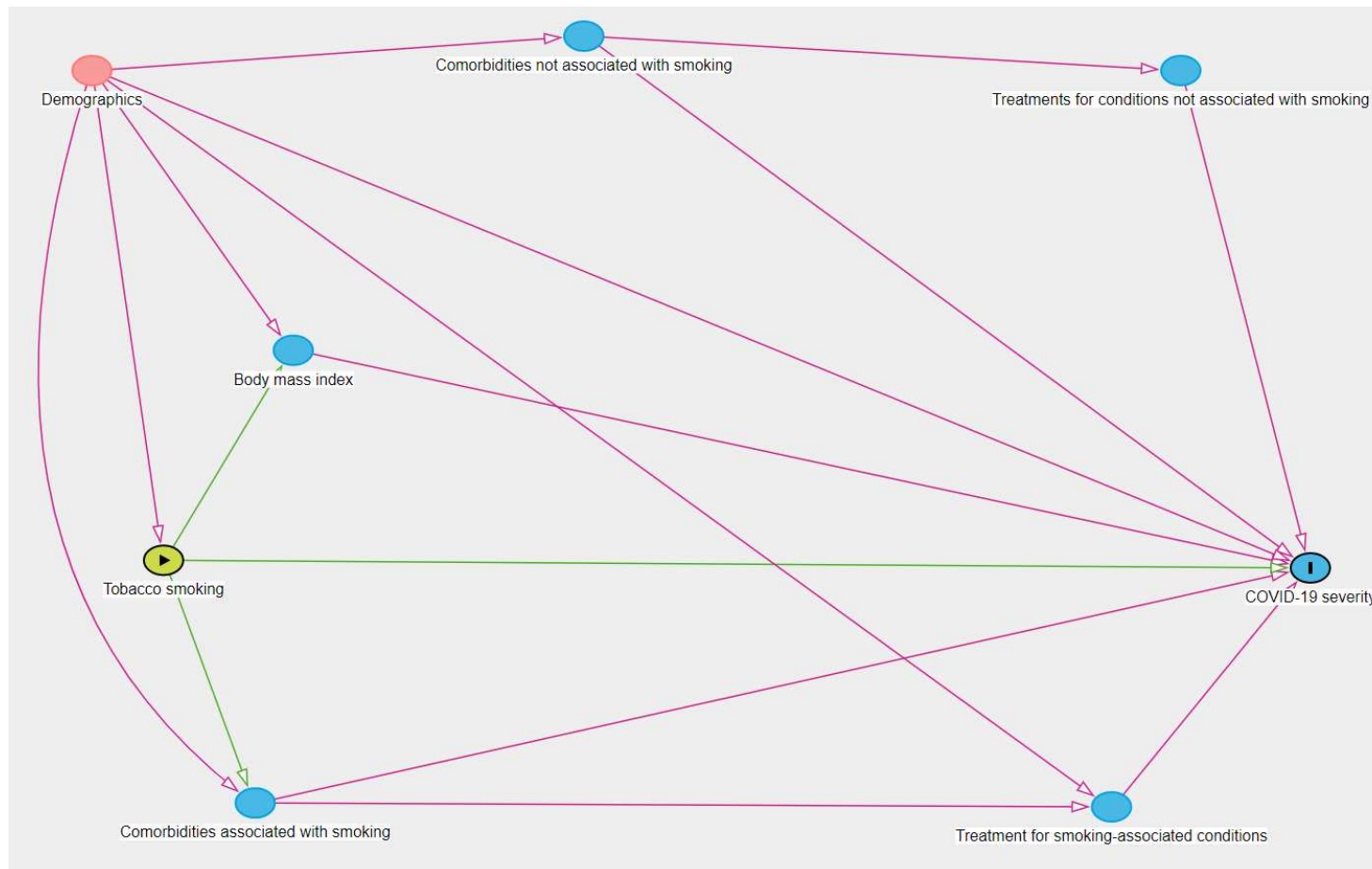
Supplementary Table 8. Sensitivity analyses of smoking behaviours on COVID-19 susceptibility and severity using SNP-exposure estimates that exclude UK Biobank and 23andMe

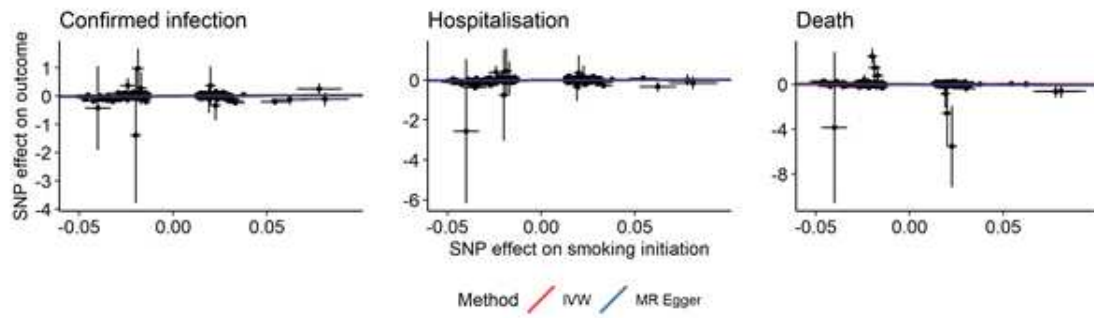
| Exposure | Outcome | MR method | OR (95% CI) | P-value |
|---------------------------------|---------------------|-------------------|--------------------|----------------|
| Smoking initiation | Confirmed infection | IVW | 2.10 (1.06-4.15) | 0.03 |
| | | MR-Egger | 0.51 (0.09-3.00) | 0.45 |
| | | Weighted median | 2.00 (0.73-5.44) | 0.18 |
| | | MR-PRESSO | 2.10 (1.06-4.15) | 0.03 |
| | Hospitalisation | IVW | 2.76 (1.17-6.50) | 0.02 |
| | | MR-Egger | 0.84 (0.09-8.05) | 0.88 |
| | | Weighted median | 2.37 (0.65-8.63) | 0.19 |
| | | MR-PRESSO | 2.76 (1.18-6.47) | 0.02 |
| | Death | IVW | 2.04 (0.60-6.96) | 0.26 |
| | | MR-Egger | 0.37 (0.01-9.49) | 0.55 |
| | | Weighted median | 2.02 (0.32-12.66) | 0.45 |
| | | MR-PRESSO | 2.04 (0.60-6.95) | 0.26 |
| Smoking heaviness (Ever smoked) | Confirmed infection | IVW | 2.45 (1.44-4.17) | <.001 |
| | | MR-Egger | 3.65 (1.60-8.28) | 0.001 |
| | | Weighted median | 3.44 (1.64-7.22) | 0.001 |
| | | MR-PRESSO | 2.45 (1.56-3.85) | <.001 |
| | Hospitalisation | IVW | 4.20 (2.18-8.08) | <.001 |
| | | MR-Egger | 6.08 (2.21-16.73) | <.001 |
| | | Weighted median | 6.85 (2.67-17.56) | <.001 |
| | | MR-PRESSO | 4.20 (2.48-7.12) | <.001 |
| | Death | IVW | 7.60 (2.99-19.31) | <.001 |
| | | MR-Egger estimate | 17.80 (4.29-73.89) | <.001 |
| | | Weighted median | 13.26 (3.71-47.46) | <.001 |
| | | MR-PRESSO | 7.60 (2.99-19.31) | <.001 |

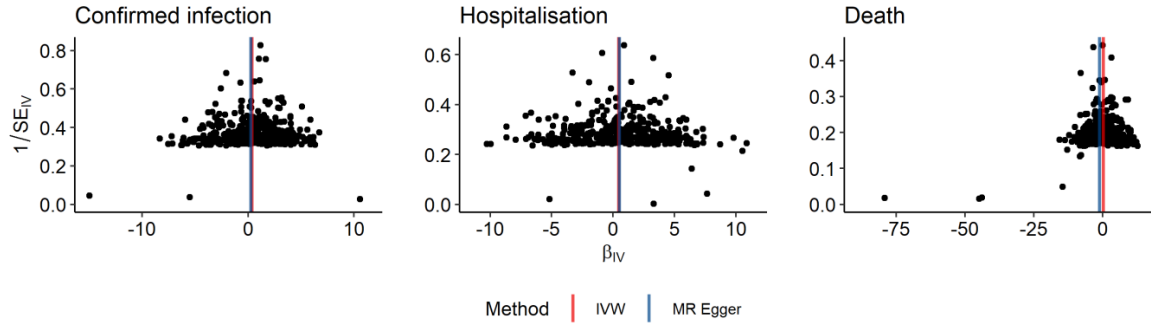
Supplementary Table 9. Sensitivity analyses of smoking behaviours on COVID-19 susceptibility and severity in 341,471 unrelated participants, unrestricted by ancestry.

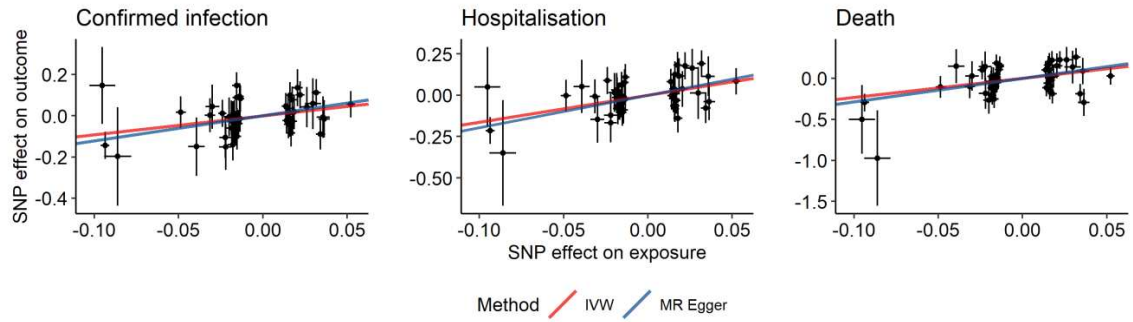
| Exposure | Outcome | MR method | OR (95% CI) | P-value |
|---------------------------------|---------------------|-------------------|---------------------|----------------|
| Smoking initiation | Confirmed infection | IVW | 1.29 (1.02-1.63) | 0.03 |
| | | MR-Egger | 1.31 (0.48-3.53) | 0.60 |
| | | Weighted median | 1.64 (1.15-2.32) | 0.01 |
| | | MR-PRESSO | 2.51 (1.28-4.89) | 0.01 |
| | Hospitalisation | IVW | 1.43 (1.05-1.94) | 0.02 |
| | | MR-Egger | 2.27 (0.62-8.29) | 0.22 |
| | | Weighted median | 1.48 (0.94-2.33) | 0.09 |
| | | MR-PRESSO | 1.43 (1.06-1.92) | 0.02 |
| | Death | IVW | 1.23 (0.79-1.92) | 0.37 |
| | | MR-Egger | 0.48 (0.07-3.16) | 0.44 |
| | | Weighted median | 1.53 (0.79-2.95) | 0.21 |
| | | MR-PRESSO | 1.23 (0.80-1.90) | 0.35 |
| Smoking heaviness (Ever smoked) | Confirmed infection | IVW | 2.06 (1.06-4.02) | 0.03 |
| | | MR-Egger | 2.51 (0.75-8.41) | 0.14 |
| | | Weighted median | 2.51 (0.85-7.42) | 0.10 |
| | | MR-PRESSO | 2.06 (1.15-3.70) | 0.02 |
| | Hospitalisation | IVW | 3.81 (1.68-8.64) | 0.00 |
| | | MR-Egger | 4.01 (0.91-17.65) | 0.07 |
| | | Weighted median | 4.38 (1.17-16.34) | 0.03 |
| | | MR-PRESSO | 3.81 (1.96-7.42) | <.001 |
| | Death | IVW | 10.35 (3.06-34.97) | <.001 |
| | | MR-Egger estimate | 27.13 (2.99-246.25) | 0.00 |
| | | Weighted median | 14.93 (2.34-95.19) | 0.00 |
| | | MR-PRESSO | 10.35 (3.06-34.97) | <.001 |

Supplementary Figure 1. Directed acyclic graph ('causal diagram') used to inform the adjustment strategy in the logistic regression models for the observational analyses. Adjustment for non-smoking-related conditions and demographic factors (age, sex, ethnicity and deprivation) may identify the 'total effect' of smoking on COVID-19 severity, hence, the first adjustment set. Body mass index and smoking-related conditions are on indirect causal pathways (coloured green) from the exposure (smoking) and the outcomes of interest, and therefore adjustment for them may enable isolation of the direct causal effect.



Supplementary Figure 2. Scatter plots for smoking initiation (378 variants)

Supplementary Figure 3. Funnel plots for smoking initiation (378 variants)

Supplementary Figure 4. Scatter plots for smoking heaviness in ever smokers (55 variants)

Supplementary Figure 5. Funnel plots for smoking heaviness in ever smokers (55 variants)