Family Socioeconomic Position and Lung Cancer Risk: A Meta-analysis and a Mendelian Randomization Study

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Research

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Abstract

Background

Family socioeconomic position (SEP) in childhood is an important factor to predict some chronic diseases. However, the association between family SEP in childhood and the risk of lung cancer is not clear.

Methods

A systematic search was performed to explore their relationship. We selected education level, socioeconomic positions of parents and childhood housing conditions to represent an individual family SEP. Hazard ratios (HRs) of lung cancer specific-mortality were synthesized using a random effects model. Two-sample Mendelian randomization (MR) was carried out with summary data from published genome-wide association studies of SEP to assess the possible causal relationship of SEP and risk of lung cancer.

Results

Through meta-analysis of 13 studies, we observed that poorer SEP was associated with increased lung cancer risk (HR: 1.25, 95% CI: 1.10, 1.43). In addition, the dose-response analysis revealed a negative correlation between SEP in childhood and lung cancer in adulthood. Same conclusion was reached in MR [(education level) OR 0.50, 95% CI: 0.39, 0.63; P : <0.001].

Conclusions

This study indicates that poor family SEP in childhood is a causal risk factor for lung cancer. We believe this population may receive greater benefit from lung cancer screening programs.

Systematic review registration

Prospero ID: 159082

Background

The relationship between everyday-life situations in childhood and chronic diseases has received increased attention across a number of disciplines in recent years.[1–4] In addition to the genetic effects, the effects of social environment in early life can also impact one's later life.[5, 6] Early prediction of high incidence of lung cancer can play an important role in preventing lung cancer-specific death. Early detection and treatment of lung cancer is a promising strategy to reduce lung cancer mortality.[7]

SEP is one of the interfering factors of health of family members. Family SEP in childhood consists of many conditions, including years of schooling, parents' social status, childhood housing conditions and so on. So far, family SEP in childhood is an increasingly important factor to predict chronic diseases. Multiple studies have indicated that there is an association between SEP and the risk of chronic disease.[8–11] Some cohort studies have also demonstrated the impact of family SEP in childhood on adult disease.[12–25] Overall, poor SEP in early years has an impact on adult morbidity and mortality, especially in cardiovascular and

gastrointestinal disorders.[26, 27] However, there has been little reliable evidence that lung cancer in adulthood may be related to family SEP in childhood.

In this study, we sought to investigate the association between SEP and lung cancer risk. A meta-analysis with dose response and a two-sample Mendelian Randomization (MR) were performed using single or multiple single nucleotide polymorphisms (SNPs) as an instrument in instrumental variable analyses by studying known genetic determinants of the exposure variable of interest.

MR uses genetic variants as instrumental variables for assessing causal relationships from observational data[28] and is an established method for probing questions of causality in observational epidemiology.[29] MR technique is being extensively applied to estimate the long-term causal effects of various exposures on clinical and epidemiological outcomes using observational data.[30] MR is an established approach to evaluate the effect of an exposure on an outcome. Most importantly, unlike main effect MR studies, gene x environment interaction studies are susceptible to confounding factors.[31]

Method

Search strategy and inclusion criteria

Two investigators (W.R., L.C.) independently searched, PubMed, Web of Science from their inceptions (1966 and 1947, respectively) to June 1, 2020, for cohort studies related to family SEP in childhood and lung cancer in adulthood, without language restrictions. Keywords used were “socioeconomic position (SEP)”, “cohort”, “lung cancer”, “risk”, as well as their Medical Subject Headings (MeSH) terms. Only papers published in English were included. Details of the search terms and inclusion/exclusion criteria are shown in Figure 1.

The inclusion criteria were: (i) cohort study design; (ii) all cases were lung cancer patients, and data were classified according to different SEP, regardless of subtypes of lung cancer; (iii) sufficient data on the association between family SEP in childhood and lung cancer in the adulthood. In addition, the exclusion criteria were: (i) small sample sizes; (ii) non-English publications; (iii) incomplete or insufficient data on the association between family SEP in childhood and lung cancer in the adulthood.

All the included studies were divided into two groups: (I) studies reported adjusted estimates of the hazard ratios (HR) (including relative risk and odds ratios) and 95% confidence interval (95%CI); (II) studies missed data mentioned above. We also included studies that graded data based on parents' financial status and family life in childhood, and overall impact. The quintile or quartile method was incorporated and the first level was used as the reference.

Data acquisition quality assessment

Data were extracted by two investigators (W.R., H.Z.) independently, and any disagreements came to consensus after discussion. Basic data were recorded from all eligible studies, including the first author's name, publication year, country, study period, period of follow-up, number of lung cancer patients and HR with their 95% CI. The results were reviewed by two senior investigators (L.W., H.J.).

Quality assessment

The quality of the studies was evaluated using a score system that was designed with reference to the Newcastle-Ottawa Scale (NOS) tool.[32-34] The system is based on a 0-9 points, with 9 reflecting the highest quality and 0 the lowest. Each point was allocated for the following: (I) representativeness of exposure arm(s), (II) selection of the comparative arm(s), (III) origin of exposure source, (IV) demonstration that outcome of interest was not present at start of study, (V) studies controlling the most important factors, (VI) studies controlling the other main factors, (VII) assessment of outcome with independency, (VIII) adequacy of follow-up length (to assess outcome), (IX) lost to follow-up acceptable (less than 10% and reported).

Two researchers (W.R. and G.F.) independently evaluated the methodological quality of each included published cohort study. The results of the quality assessment were used for descriptive purposes, to provide an overall assessment of the quality of the included studies.[32, 35-38]

Statistical analyses in Meta-analysis

A meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[39, 40] We collected study-specific HR with 95%CI for lung cancer to combine the data. Through Cochran's I^2 statistic, we examined the heterogeneity across studies and statistical heterogeneity was considered if an I^2 statistic $\geq 50\%$. A random effect model was employed to synthesize hazard ratios (HRs) for lung cancer-specific mortality if high heterogeneity existed ($p < 0.5$, $I^2 > 50\%$), otherwise a fixed effect model was conducted.

We utilized Funnel plot tests, Begg's test and Egger's test to evaluate the publication bias. [41-43] In addition, subgroup analyses were performed based on genders and data. Sensitivity analysis was conducted by excluding each study in turn to assess the stability of results and potential sources of heterogeneity. All statistical manipulation was employed by Stata software (version 12, StataCorp, TX, USA). All P values were 2-tailed; statistical significance was set at P value < 0.05 . [44]

The dose-response study was analyzed by Benchmark Dose Software 3.1.2 (BMDS 3.1.2). [45] All steps were established under the BMDS guidelines. [46-49] Multiple models were selected for analysis, including extra risk assumptions for background and a benchmark response of 5%. [33, 34] According to the included studies, the dose response was divided into two categories: family economic status in childhood and childhood housing conditions. At the same time, according to the original data with or without adjustment, it was divided into adjusted and unadjusted group for subgroup analysis and publication bias analysis. In all dose-response models, we used Exponential models and Hill models as the main dose-response observation results, [50] while using other results for verification. Duplicate studies were excluded.

MR Analysis Using Summary Statistics

The MR method was based on the following three assumptions: (i) the instrumental variables are strongly associated with the family SEP in childhood; (ii) the instrumental variables affect cancer only through their

effect on family SEP in childhood and not through any alternative causal pathway; and (iii) the instrumental variables are independent of any confounders.[51, 52] To assess the potential violation of these assumptions, we evaluated the directional pleiotropy based on the intercept obtained from the MR Egger analysis.[53] We also performed a leave-one-out analysis in which we sequentially omitted one SNP at a time, to evaluate whether the MR estimate was driven or biased by a single SNP.

The analysis was conducted to estimate the effect of family SEP in childhood (X) on the risk of lung cancer (Y) using genetic variants (g), and the causal estimate is equal to Yg/Xg [54]. For the association between genetic variants and family SEP in childhood (Xg), summary data were utilized from published Genome-Wide Association Studies (GWASs),[55-70] including Social Science Genetic Association Consortium (SSGAC) (1,060,068 individuals), [MRC Integrative Epidemiology Unit](#) (MRC-IEU)(249,790 individuals), UK Biobank(75,244 individuals) and Neale Lab (455,571 individuals)(Supplement Table 1).[71-73] Summary statistics for the association between genetic variants and lung cancer (Yg) are from the International Lung Cancer Consortium (ILCCO) (27,209 individuals) (Supplement Table 2). [62]

We selected uncorrelated variants to construct the instrumental variables in the two-sample MR analysis. Using both summary statistics for Yg and Xg , an Inverse Variance-Weighted (IVW) meta-analysis was employed to estimate the effect of genetically determined family SEP in childhood on the risk of lung cancer using the method of Burgess et al.[74]:

$$\hat{\beta}_{IVW} = \frac{\sum_{i=1}^g X_g Y_g \sigma_{Yg}^{-2}}{\sum_{i=1}^g X_g^2 \sigma_{Yg}^{-2}}, se(\hat{\beta}_{IVW}) = \sqrt{\frac{1}{\sum_{i=1}^g X_g^2 \sigma_{Yg}^{-2}}}$$

where Xg is the beta estimate for the association between the SNP and family SEP in childhood, Yg is the beta estimate for the association between the SNP and lung cancer, and σ_{Yg} is the standard error for Yg . Corresponding HR and 95% CIs were calculated using $\hat{\beta}_{IVW}$ and $se(\hat{\beta}_{IVW})$.

In addition, MR-Egger and Weighted Median were also conducted to identify the causality. Ward ratio would only be observed when the first three models cannot be used due to lack of SNPs.[75] Leave-one-out analysis was conducted to estimate whether the result was driven by a single SNP. MR-Egger regression was also performed to access the pleiotropy.

Result

Family socioeconomic position in childhood and the risk of lung cancer in adulthood observational analyses

A total of thirteen cohort studies consisting of 2,779,242 cases were included,[13–16, 18–24]. Among them, eight studies met the inclusion criteria and were included in the present meta-analysis[12, 13, 16, 19–24] and seven studies were included in the dose-response analysis.[12–18] The characteristics of these studies can be

seen in Supplement Table 3. The age of the included investigators ranged from 14–74 (a group of missing), the majority of the respondents were between the age of 30–64 with 2413 respondents recorded to have died from lung cancer. Supplement Table 4 presented the result of the quality assessment. Results and study characteristics including name of first author, publication year, country or region, follow-up period, sample size and number of cases or deaths, type of outcome, gender, age range, HRs and 95% CIs were extracted and can be seen in Supplement Table 5.

The results of quality assessment did not suggest any evidence of publication bias (Supplement Fig. 1,2). [Unadjusted group: (Begg: 0.673; Egger: 0.182)]; [Adjusted group: (Begg:1; Egger:0.228)]. And sensitivity analysis was performed by sequentially excluding individual studies. (Supplement Fig. 3,4)

In unadjusted group, the pooled HR for family economy conditions with best family SEP in childhood group was 1.42 (95% CI, 1.21, 1.66) (I2 = 73.4%, P < 0.001) (Table 1, Fig. 3). The risk was slightly lower than adjusted group: 1.25 (95% CI, 1.10, 1.42) (I2 = 48.9%, P = 0.04) (Table 1, Fig. 4). Subgroup analysis based on sex using the provided adjusted original data resulted in a pooled HR of 1.09 (95% CI 0.95, 1.26) (I2 = 0.0%, p = 0.78) for male, a pooled HR of 1.10 (95%CI 0.88, 1.35) (I2 = 0.0%, p = 0.57) for female, and a pooled HR of 1.39 (95%CI 1.20, 1.62) (I2 = 48.9%, p = 0.04) for both sexes. Subgroup analysis based on sex that provided unadjusted original data resulted in a pooled HR of 1.52 (95% CI 1.13, 2.06) (I2 = 87.1%, p = 0.006) for male and a pooled HR of 1.28 (95%CI 1.07, 1.54) (I2 = 19.4%, p = 0.007) for female and a pooled HR of 1.63 (95%CI 1.15, 2.32) (I2 = 58.7%, p = 0.006) for both sexes. The above results was consistent in dose response used the model summary with BMR of 1 Std. Dev. including the family economic conditions of parents and childhood housing conditions (Fig. 2).

Table 1
Pooled Estimates from Random Effects Meta-Analysis, Expressing the HR of risk of lung cancer.

Outcome	Adjusted group			Unadjusted group		
	HR (95%CI)	P-value	ι ²	HR (95%CI)	P-value	ι ²
Overall	1.25 (1.10–1.43)	0.04	48.90%	1.42 (1.21–1.66)	<0.001	73.40%
Male	1.10 (0.96-1.26)	0.78	0.00%	1.52 (1.13-2.06)	0.01	87.10%
Female	1.09 (0.88-1.35)	0.57	0.00%	1.28 (1.07-1.54)	0.01	19.40%
Both sexes	1.40 (1.20-1.62)	0.04	48.80%	1.63 (1.15-2.32)	0.01	58.70%
(HR: Hazard Ratio)						

Genetically determined family SEP in childhood was associated with risk of lung cancer in adulthood

Genetically predicted lower family SEP in childhood was associated with significantly higher odds of lung cancer (Table 2). The causal relationship between length of education and lung cancer was verified first.

Using conventional MR analysis, one SD longer education was associated with a 50% lower risk of lung cancer (SSGAC 1: OR 0.50, 95% CI: 0.39, 0.63; P : 0.001). Another gene pool with the same exposure factor was also included for verification in our study, showing one SD longer education (genetic predisposition by 4 SNPs) was associated with a 60% lower risk of lung cancer (SSGAC 2: OR 0.40, 95% CI 0.32, 0.50; p : 0.001). With a sample size of 27 209, our sample provided sufficient statistical power (greater than 80%) to detect a causal effect of educational attainment on lung cancer. Power calculations on MR analysis were performed according to Brion *et al.*[76]

Table 2

Mendelian randomization estimates of the associations between family SEP in childhood and risk of lung cancer.

Outcome	Inverse variance weighted		Weighted median		MR Egger		Ward Ratio	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
The associations between education attainment and risk of lung cancer overall and histological types (Okbay <i>et al</i>)								
Lung Cancer Overall	0.49(0.35-0.69)	<0.01	0.60(0.39-0.91)	0.02	0.65(0.11-3.81)	0.63	N/A	N/A
Lung Adenocarcinoma	0.64(0.41-1.02)	0.06	0.66(0.36-1.20)	0.17	1.35(0.12-14.80)	0.80	N/A	N/A
Squamous Cell Lung Cancer	0.40(0.26-0.62)	0.00	0.53(0.29-0.97)	0.04	0.20(0.02-1.89)	0.16	N/A	N/A
The associations between education attainment and risk of lung cancer overall and histological types (Lee <i>et al</i>)								
Lung Cancer Overall	0.42(0.28-0.62)	<0.05	0.66(0.51-0.76)	0.016	0.82(0.54-1.25)	0.63	N/A	N/A
Lung Adenocarcinoma	0.23(0.08-0.67)	0.06	0.38(0.19-0.76)	0.17	0.58(0.20-1.65)	0.80	N/A	N/A
Squamous Cell Lung Cancer	0.40(0.31-0.52)	<0.01	0.55(0.46-0.65)	0.04	0.74(0.57-0.96)	0.16	N/A	N/A
The associations between father's age at death and risk of lung cancer overall and histological types								
Lung Cancer Overall	N/A	N/A	N/A	N/A	N/A	N/A	2.15E-05(1.42E-06-3.26E-04)	<0.01
Lung Adenocarcinoma	N/A	N/A	N/A	N/A	N/A	N/A	1.77E-05(3.00E-06-1.04E-04)	<0.01
Squamous Cell Lung Cancer	N/A	N/A	N/A	N/A	N/A	N/A	3.39E-05(2.33E-06-4.93E-04)	<0.01
(OR = Odds Ratio, N/A = Not available)								

Meanwhile, associations were consistent in sensitivity analyses using weighted median (OR 0.57, 95% CI 0.45, 0.71; P : 0.001; Okbay *et al*) (OR 0.58, 95% CI 0.48, 0.70; P : <0.001; Lee *et al*) and MR-Egger method (OR 0.56, 95% CI 0.17, 1.88; P : 0.35; Okbay *et al*) (OR 0.75, 95% CI 0.60, 0.94; P : 0.01; Lee *et al*), but provided less precise estimates than with conventional MR (IVW method). Nonetheless, their causal estimates were similar in terms

of direction and magnitude, and they were unlikely to occur by chance alone. These results were consistent with the hypothesis that genetic pleiotropy does not drive the result.

We also analyzed and observed the relationship between other exposure factors related to family SEP in childhood and lung cancer, and we found that the P-values for the intercept were large and the estimates adjusted for pleiotropy suggested null effects in four exposure factors: number of children fathered (Neale Lab): (OR 0.92, 95% CI: 0.29, 2.84; p : 0.88); mother's age at death (Neale Lab): (OR 1.00, 95% CI: 0.19, 5.26; p : 1.00); and average total household income before tax (MRC-IEU): (OR 0.90, 95% CI: 0.77, 1.04; p : 0.156). Nine out of the fifteen independent exposure factor gene pools were unable to be analyzed due to the lack of SNPs corresponding to lung cancer.

Discussion

Based on data from 2,779,242 respondents, we observed that poorer family SEP in childhood means higher lung cancer risk in adulthood compared to controls. The overall dose-response of multiple models also demonstrated this trend. This phenomenon was partially verified by Mendelian randomization of two samples, but the causal relationship between some genes was still unclear. Through meta-analysis, we analyzed both the adjusted (age/adult social class) and unadjusted data, and strengthened the credibility by mutual authentication. The results showed a link between family SEP in childhood and the risk of lung cancer in adulthood in the unadjusted group.

People in poor family economic conditions were more likely to smoke, leading to a higher risk of lung cancer. [77] Furthermore, the poor face a variety of problems that may pose other risks including malnutrition, violence, AIDS, and other infectious diseases, which also correlate with lung cancer risk. [78, 79] The dose-response curve of family SEP in childhood also contribute to risk. Specifically, the lower the family economic conditions in childhood and the worse the childhood housing conditions, the more likely a person is to develop lung cancer in adulthood. This result has been verified in both the adjusted and unadjusted groups. We selected factors as comprehensive as possible to explore the relationship between family SEP in childhood and the risk of lung cancer in adulthood using two sample MR. Only the data from the official database were used, which made our data more reliable and useful. The results show that there is a clear causal relationship between the length of education and the occurrence of lung cancer. People with low education during childhood were more likely to smoke or be exposed to undesirable living environments, and lack relevant basic medical knowledge. Moreover, Children of parents who smoke perceived casual smoking to be safer and then reported wanting to smoke in response to smoking-related cues more than children of non-smoking parents. [80] It should be noted that further research is needed to prove the relationship between father's age of death and lung cancer. On the one hand, although our results showed a strong correlation between SEP and the risk of lung cancer, only one SNP was included. This is too small to calculation of explained variance. This limited the representativeness of the result of father's death of age and lung cancer. On the other hand, early parental death, when a child experiences the loss of a parent before age 18, is one of the most severe stressors and a potential risk factor for adult psychopathology.[81]It may cause an increased likelihood of poor habits, for example, smoking, which in turn lead to lung cancer. Worth mentioning, among the results related to education duration, the results of incorporating the genome determined by Okbay et al. were slightly different from the previous results of Zhou et al[82]. This may be explained by these observations: the statistical

significance was set as P-value < 0.001 instead of 0.01 in the R package used for two-sample MR.[28, 83] Because of this, the positive results of our study are more reliable. For the negative result in two-sample Mendelian randomization, we believe that further researcher is required to verify the result. Because the data of the SNPs in the existing studies are still limited, the final results of these studies have not yet been proven.

Three strengths of our study should be highlighted. First, to our knowledge, this is the most comprehensive meta-analysis estimating the relationship between family economic position in childhood and the risk of lung cancer in adulthood. The collection of such large sample data to assess the cancer risk for different family SEP in childhood around the world has not previously been performed. Second, we included adjusted and non-adjusted data for all-factors to mutually verify the dose-response of parents' socioeconomic status and family congestion in childhood. Third, this is the first study to explore the causal relationship between family SEP in childhood and the risk in adulthood by two sample MR. This research offered evidence for researcher focus on epidemiological characters in early detection of lung cancer and clinical staff of early diagnosis of lung cancer.

There are several limitations in our study. First, the studies included have geographical limitations. The studies included for meta-analysis and dose-response studies originated from the UK, Norway, and the Netherlands. Second, because of the long-term follow-up needs of this study, included studies do not have data from recent years. Third, because the included cohort studies were all-factor epidemiological studies, subgroups of different lung cancer subtypes could not be established. Fourth, in terms of meta-analysis, due to the lack of subgroup data, the results obtained by the adjusted male and female subgroups were not statistically significant. Another potential limitation is that we only included common polymorphisms. Finally, although we have included many different exposure genes to build connections with lung cancer gene pool, some Mendelian randomization results are negative. However, limited SNPs of SEP can lead to false negative result. Further verification is needed to make a precise conclusion for the reason given above.

This research needs to be improved. Cohort results from other countries and expanded observations from lung cancer to all-factor risk are necessary for future studies. Genetic characteristics of continents other than Europe should also be included. Overall, our research confirms our conjecture: the family SEP in childhood is inversely proportional to the risk of lung cancer, which has a positive effect on the early diagnosis and intervention of lung cancer.

Conclusion

This study indicates that poor family SEP in childhood is a causal risk factor for lung cancer, and thus lung cancer screening should be more heavily considered for these populations. More research is needed to cross-validate these findings.

Abbreviations

CI	Confidence interval
GWASs	Genome-wide association studies
HR	Hazard ratio
ILCCO	International Lung Cancer Consortium
IVW	Inverse Variance-Weighted
MeSH	Medical Subject Headings
MR	Mendelian randomization
OR	Odds ratios
RR	Relative risk
SCLC	Small cell lung cancer
SNP	Single-nucleotide polymorphism
TSMR	Two-sample Mendelian randomization
BMDS	Benchmark Dose Software

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

H.J. and L.W. conceived of and designed the study. W.R., L.C. and H.Z. developed the methodology. G.F., J.Y., W.Y., S.Z., L.H., C.B., L.J., X.S., F.Y. acquired the data. L.W. and W.R. analyzed and interpreted the data. L.W., W.R., Z.R., wrote the manuscript.

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References

1. Hertzman C: **The biological embedding of early experience and its effects on health in adulthood.** *Ann N Y Acad Sci* 1999, **896**:85-95.
2. Carey G, Crammond B: **Systems change for the social determinants of health.** *BMC public health* 2015, **15**:662.
3. Blackwell DL, Hayward MD, Crimmins EM: **Does childhood health affect chronic morbidity in later life?** *Social science & medicine (1982)* 2001, **52**(8):1269-1284.
4. Nordestgaard AT, Thomsen M, Nordestgaard BG: **Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study.** *International journal of epidemiology* 2015, **44**(2):551-565.
5. Mackenbach JP, Kulhánová I, Bopp M, Deboosere P, Eikemo TA, Hoffmann R, Kulik MC, Leinsalu M, Martikainen P, Menvielle G *et al*: **Variations in the relation between education and cause-specific mortality in 19 European populations: a test of the "fundamental causes" theory of social inequalities in health.** *Soc Sci Med* 2015, **127**:51-62.
6. Oates GR, Schechter MS: **Socioeconomic status and health outcomes: cystic fibrosis as a model.** *Expert Rev Respir Med* 2016, **10**(9):967-977.
7. Yee J, Sadar MD, Sin DD, Kuzyk M, Xing L, Kondra J, McWilliams A, Man SFP, Lam S: **Connective tissue-activating peptide III: a novel blood biomarker for early lung cancer detection.** *J Clin Oncol* 2009, **27**(17):2787-2792.
8. Disano J, Goulet J, Muhajarine N, Neudorf C, Harvey J: **Social-economic status and rates of hospital admission for chronic disease in urban Canada.** *Can Nurse* 2010, **106**(1):24-29.
9. Kalyesubula R, Nankabirwa JI, Ssinabulya I, Siddharthan T, Kayima J, Nakibuuka J, Salata RA, Mondo C, Kanya MR, Hricik D: **Kidney disease in Uganda: a community based study.** *BMC Nephrol* 2017, **18**(1):116-

10. Forootan M, Bagheri N, Darvishi M: **Chronic constipation: A review of literature.** *Medicine (Baltimore)* 2018, **97**(20):e10631-e10631.
11. Yankson R, Anto EA, Chipeta MG: **Geostatistical analysis and mapping of malaria risk in children under 5 using point-referenced prevalence data in Ghana.** *Malar J* 2019, **18**(1):67-67.
12. Frankel S, Gunnell DJ, Peters TJ, Maynard M, Davey Smith G: **Childhood energy intake and adult mortality from cancer: the Boyd Orr Cohort Study.** *Bmj* 1998, **316**(7130):499-504.
13. Smith GD, Hart C, Blane D, Hole D: **Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study.** *Bmj* 1998, **316**(7145):1631-1635.
14. Hart CL, Davey Smith G: **Relation between number of siblings and adult mortality and stroke risk: 25 year follow up of men in the Collaborative study.** *J Epidemiol Community Health* 2003, **57**(5):385-391.
15. Power C, Hypponen E, Smith GD: **Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort.** *Am J Public Health* 2005, **95**(8):1396-1402.
16. Galobardes B, Davey Smith G, Jeffreys M, McCarron P: **Childhood socioeconomic circumstances predict specific causes of death in adulthood: the Glasgow student cohort study.** *J Epidemiol Community Health* 2006, **60**(6):527-529.
17. de Kok IM, van Lenthe FJ, Avendano M, Louwman M, Coebergh JW, Mackenbach JP: **Childhood social class and cancer incidence: results of the globe study.** *Soc Sci Med* 2008, **66**(5):1131-1139.
18. Dedman DJ, Gunnell D, Davey Smith G, Frankel S: **Childhood housing conditions and later mortality in the Boyd Orr cohort.** *J Epidemiol Community Health* 2001, **55**(1):10-15.
19. Claussen B, Davey Smith G, Thelle D: **Impact of childhood and adulthood socioeconomic position on cause specific mortality: the Oslo Mortality Study.** *J Epidemiol Community Health* 2003, **57**(1):40-45.
20. Naess O, Claussen B, Davey Smith G: **Relative impact of childhood and adulthood socioeconomic conditions on cause specific mortality in men.** *J Epidemiol Community Health* 2004, **58**(7):597-598.
21. Metcalfe C, Davey Smith G, Sterne JA, Heslop P, Macleod J, Hart CL: **Cause-specific hospital admission and mortality among working men: association with socioeconomic circumstances in childhood and adult life, and the mediating role of daily stress.** *Eur J Public Health* 2005, **15**(3):238-244.
22. Lawlor DA, Sterne JA, Tynelius P, Davey Smith G, Rasmussen F: **Association of childhood socioeconomic position with cause-specific mortality in a prospective record linkage study of 1,839,384 individuals.** *Am J Epidemiol* 2006, **164**(9):907-915.
23. Naess O, Claussen B, Smith GD: **Housing conditions in childhood and cause-specific adult mortality: the effect of sanitary conditions and economic deprivation on 55,761 men in Oslo.** *Scand J Public Health* 2007, **35**(6):570-576.
24. Strand BH, Kunst A: **Childhood socioeconomic position and cause-specific mortality in early adulthood.** *Am J Epidemiol* 2007, **165**(1):85-93.
25. Melchior M, Berkman LF, Kawachi I, Krieger N, Zins M, Bonenfant S, Goldberg M: **Lifelong socioeconomic trajectory and premature mortality (35-65 years) in France: findings from the GAZEL Cohort Study.** *Journal of epidemiology and community health* 2006, **60**(11):937-944.

26. Galobardes B, Smith GD, Lynch JW: **Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood.** *Ann Epidemiol* 2006, **16**(2).
27. Vohra J, Marmot MG, Bauld L, Hiatt RA: **Socioeconomic position in childhood and cancer in adulthood: a rapid-review.** *Journal of epidemiology and community health* 2016, **70**(6):629-634.
28. Yavorska OO, Burgess S: **MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data.** *International journal of epidemiology* 2017, **46**(6):1734-1739.
29. Bowden J, Del Greco M F, Minelli C, Davey Smith G, Sheehan NA, Thompson JR: **Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I² statistic.** *International journal of epidemiology* 2016, **45**(6):1961-1974.
30. Burgess S, Daniel RM, Butterworth AS, Thompson SG: **Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways.** *International journal of epidemiology* 2015, **44**(2):484-495.
31. Tyrrell J, Wood AR, Ames RM, Yaghootkar H, Beaumont RN, Jones SE, Tuke MA, Ruth KS, Freathy RM, Davey Smith G *et al.*: **Gene-obesogenic environment interactions in the UK Biobank study.** *International journal of epidemiology* 2017, **46**(2):559-575.
32. Stang A: **Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.** *Eur J Epidemiol* 2010, **25**(9):603-605.
33. Bogen KT: **Generic Hockey-Stick Model for Estimating Benchmark Dose and Potency: Performance Relative to BMDS and Application to Anthraquinone.** *Dose Response* 2011, **9**(2):182-208.
34. Haber LT, Dourson ML, Allen BC, Hertzberg RC, Parker A, Vincent MJ, Maier A, Boobis AR: **Benchmark dose (BMD) modeling: current practice, issues, and challenges.** *Crit Rev Toxicol* 2018, **48**(5):387-415.
35. Friedemann Smith C, Tompson A, Holtman GA, Bankhead C, Gleeson F, Lasserson D, Nicholson BD: **General practitioner referrals to one-stop clinics for symptoms that could be indicative of cancer: a systematic review of use and clinical outcomes.** *Fam Pract* 2019, **36**(3):255-261.
36. Lo CK-L, Mertz D, Loeb M: **Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments.** *BMC Med Res Methodol* 2014, **14**:45-45.
37. Wang F-G, Yan W-M, Yan M, Song M-M: **Outcomes of Mini vs Roux-en-Y gastric bypass: A meta-analysis and systematic review.** *Int J Surg* 2018, **56**:7-14.
38. Wells. G, Shea. B, O'Connell. D, Peterson. J, Welch. V, Losos. M, Tugwell. P: **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.**
39. Bernardo WM: **PRISMA statement and PROSPERO.** *Int Braz J Urol* 2017, **43**(3):383-384.
40. Selçuk AA: **A Guide for Systematic Reviews: PRISMA.** *Turk Arch Otorhinolaryngol* 2019, **57**(1):57-58.
41. Fan D, Liu L, Xia Q, Wang W, Wu S, Tian G, Liu Y, Ni J, Wu S, Guo X *et al.*: **Female alcohol consumption and fecundability: a systematic review and dose-response meta-analysis.** *Scientific reports* 2017, **7**(1):13815.
42. Lin L, Chu H: **Quantifying publication bias in meta-analysis.** *Biometrics* 2018, **74**(3):785-794.
43. Shi L, Lin L: **The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses.** *Medicine (Baltimore)* 2019, **98**(23):e15987-e15987.

44. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: **Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.** *JAMA* 2000, **283**(15):2008-2012.
45. Jensen SM, Kluxen FM, Ritz C: **A Review of Recent Advances in Benchmark Dose Methodology.** *Risk Anal* 2019, **39**(10):2295-2315.
46. Shao K, Shapiro AJ: **A Web-Based System for Bayesian Benchmark Dose Estimation.** *Environmental health perspectives* 2018, **126**(1):017002.
47. Filipsson AF, Sand S, Nilsson J, Victorin K: **The benchmark dose method—review of available models, and recommendations for application in health risk assessment.** *Crit Rev Toxicol* 2003, **33**(5):505-542.
48. Davis JA, Gift JS, Zhao QJ: **Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1.** *Toxicol Appl Pharmacol* 2011, **254**(2):181-191.
49. Agency. USEP: **BMDS Wizard User's Guide.** 2015.1.
50. Ma J: **Estimating epidemic exponential growth rate and basic reproduction number.** *Infect Dis Model* 2020, **5**:129-141.
51. Boef AGC, Dekkers OM, le Cessie S: **Mendelian randomization studies: a review of the approaches used and the quality of reporting.** *International journal of epidemiology* 2015, **44**(2):496-511.
52. Burgess S, Dudbridge F, Thompson SG: **Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods.** *Stat Med* 2016, **35**(11):1880-1906.
53. Burgess S, Thompson SG: **Interpreting findings from Mendelian randomization using the MR-Egger method.** *Eur J Epidemiol* 2017, **32**(5):377-389.
54. Ordóñez-Mena JM, Schöttker B, Mons U, Jenab M, Freisling H, Bueno-de-Mesquita B, O'Doherty MG, Scott A, Kee F, Stricker BH *et al*: **Quantification of the smoking-associated cancer risk with rate advancement periods: meta-analysis of individual participant data from cohorts of the CHANCES consortium.** *BMC Med* 2016, **14**:62.
55. Tang H, Wei P, Chang P, Li Y, Yan D, Liu C, Hassan M, Li D: **Genetic polymorphisms associated with pancreatic cancer survival: a genome-wide association study.** *Int J Cancer* 2017, **141**(4):678-686.
56. Astle WJ, Elding H, Jiang T, Allen D, Ruklisa D, Mann AL, Mead D, Bouman H, Riveros-Mckay F, Kostadima MA *et al*: **The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease.** *Cell* 2016, **167**(5).
57. Lutz SM, Cho MH, Young K, Hersh CP, Castaldi PJ, McDonald M-L, Regan E, Mattheisen M, DeMeo DL, Parker M *et al*: **A genome-wide association study identifies risk loci for spirometric measures among smokers of European and African ancestry.** *BMC Genet* 2015, **16**:138.
58. Wheeler HE, Gamazon ER, Frisina RD, Perez-Cervantes C, El Charif O, Mapes B, Fossa SD, Feldman DR, Hamilton RJ, Vaughn DJ *et al*: **Variants in and Other Mendelian Deafness Genes Are Associated with Cisplatin-Associated Ototoxicity.** *Clin Cancer Res* 2017, **23**(13):3325-3333.
59. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J *et al*: **Genetic studies of body mass index yield new insights for obesity biology.** *Nature* 2015, **518**(7538):197-206.

60. Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, Benlloch S, Hazelett DJ, Wang Z, Saunders E *et al*: **A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer.** *Nat Genet* 2014, **46**(10):1103-1109.
61. Broer L, Buchman AS, Deelen J, Evans DS, Faul JD, Lunetta KL, Sebastiani P, Smith JA, Smith AV, Tanaka T *et al*: **GWAS of longevity in CHARGE consortium confirms APOE and FOXO3 candidacy.** *J Gerontol A Biol Sci Med Sci* 2015, **70**(1):110-118.
62. Wang Y, McKay JD, Rafnar T, Wang Z, Timofeeva MN, Broderick P, Zong X, Laplana M, Wei Y, Han Y *et al*: **Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer.** *Nat Genet* 2014, **46**(7):736-741.
63. Mayerle J, den Hoed CM, Schurmann C, Stolk L, Homuth G, Peters MJ, Capelle LG, Zimmermann K, Rivadeneira F, Gruska S *et al*: **Identification of genetic loci associated with Helicobacter pylori serologic status.** *JAMA* 2013, **309**(18):1912-1920.
64. Lauc G, Huffman JE, Pučić M, Zgaga L, Adamczyk B, Mužinić A, Novokmet M, Polašek O, Gornik O, Krištić J *et al*: **Loci associated with N-glycosylation of human immunoglobulin G show pleiotropy with autoimmune diseases and haematological cancers.** *PLoS Genet* 2013, **9**(1):e1003225.
65. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, Willer CJ, Jackson AU, Vedantam S, Raychaudhuri S *et al*: **Hundreds of variants clustered in genomic loci and biological pathways affect human height.** *Nature* 2010, **467**(7317):832-838.
66. **Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls.** *Nature* 2007, **447**(7145):661-678.
67. Wu C, Kraft P, Stolzenberg-Solomon R, Steplowski E, Brotzman M, Xu M, Mudgal P, Amundadottir L, Arslan AA, Bueno-de-Mesquita HB *et al*: **Genome-wide association study of survival in patients with pancreatic adenocarcinoma.** *Gut* 2014, **63**(1):152-160.
68. Radstake TRDJ, Gorlova O, Rueda B, Martin J-E, Alizadeh BZ, Palomino-Morales R, Coenen MJ, Vonk MC, Voskuyl AE, Schuerwegh AJ *et al*: **Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus.** *Nat Genet* 2010, **42**(5):426-429.
69. Allanore Y, Saad M, Dieudé P, Avouac J, Distler JHW, Amouyel P, Matucci-Cerinic M, Riemekasten G, Airo P, Melchers I *et al*: **Genome-wide scan identifies TNIP1, PSORS1C1, and RHOB as novel risk loci for systemic sclerosis.** *PLoS Genet* 2011, **7**(7):e1002091.
70. Gorlova O, Martin J-E, Rueda B, Koeleman BPC, Ying J, Teruel M, Diaz-Gallo L-M, Broen JC, Vonk MC, Simeon CP *et al*: **Identification of novel genetic markers associated with clinical phenotypes of systemic sclerosis through a genome-wide association strategy.** *PLoS Genet* 2011, **7**(7):e1002178.
71. Benyamin B, Pourcain B, Davis OS, Davies G, Hansell NK, Brion MJA, Kirkpatrick RM, Cents RAM, Franić S, Miller MB *et al*: **Childhood intelligence is heritable, highly polygenic and associated with FBNP1L.** *Mol Psychiatry* 2014, **19**(2):253-258.
72. Pilling LC, Atkins JL, Bowman K, Jones SE, Tyrrell J, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Wood AR *et al*: **Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants.** *Aging (Albany NY)* 2016, **8**(3):547-560.

73. Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, Nguyen-Viet TA, Bowers P, Sidorenko J, Karlsson Linnér R *et al*: **Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals.** *Nat Genet* 2018, **50**(8):1112-1121.
74. Burgess S, Butterworth A, Thompson SG: **Mendelian randomization analysis with multiple genetic variants using summarized data.** *Genet Epidemiol* 2013, **37**(7):658-665.
75. Pierce BL, Burgess S: **Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators.** *American journal of epidemiology* 2013, **178**(7):1177-1184.
76. Brion M-JA, Shakhbazov K, Visscher PM: **Calculating statistical power in Mendelian randomization studies.** *International journal of epidemiology* 2013, **42**(5):1497-1501.
77. Chae DH, Gavin AR, Takeuchi DT: **Smoking prevalence among asian americans: findings from the National Latino and Asian American Study (NLAAS).** *Public Health Rep* 2006, **121**(6):755-763.
78. Pampel FC: **Patterns of tobacco use in the early epidemic stages: Malawi and Zambia, 2000-2002.** *American journal of public health* 2005, **95**(6):1009-1015.
79. Stubbs B, Veronese N, Vancampfort D, Prina AM, Lin P-Y, Tseng P-T, Evangelou E, Solmi M, Kohler C, Carvalho AF *et al*: **Perceived stress and smoking across 41 countries: A global perspective across Europe, Africa, Asia and the Americas.** *Scientific reports* 2017, **7**(1):7597-7597.
80. Faletau J, Glover M, Nosa V, Pienaar F: **Looks like smoking, is it smoking?: children's perceptions of cigarette-like nicotine delivery systems, smoking and cessation.** *Harm Reduct J* 2013, **10**:30-30.
81. Misra S, Gelaye B, Koenen KC, Williams DR, Borba CPC, Quattrone D, Di Forti M, La Cascia C, La Barbera D, Tarricone I *et al*: **Early Parental Death and Risk of Psychosis in Offspring: A Six-Country Case-Control Study.** *J Clin Med* 2019, **8**(7):1081.
82. Zhou H, Zhang Y, Liu J, Yang Y, Fang W, Hong S, Chen G, Zhao S, Zhang Z, Shen J *et al*: **Education and lung cancer: a Mendelian randomization study.** *Int J Epidemiol* 2019, **48**(3):743-750.
83. Burgess S: **Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome.** *International journal of epidemiology* 2014, **43**(3):922-929.

Figures

Figure 1

Flow Diagram Detailing the Search Strategy and Identification of Studies Used in Meta-analysis.

Figure 2

Dose response of childhood housing conditions and lung cancer (adjusted group) (top left), family economic conditions and lung cancer (adjusted group) (top right), childhood housing conditions and lung cancer (unadjusted group) (bottom left), family economic conditions and lung cancer (unadjusted group) (bottom right).

Figure 3

Forest plot of population-based cohort studies of family SEP and lung cancer, stratified by sex (unadjusted group).

Figure 4

Forest plot of population-based cohort studies of family SEP and lung cancer, stratified by sex (adjusted group).

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