Title

Investigating the Association Between Uncommon Exposures and Rare Disease Outcomes: an Application of a Simulation Approach to Extremely Low Frequency Magnetic Field (ELF-MF) and Childhood Leukemia

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Investigating the Association Between Uncommon Exposures and Rare Disease Outcomes: an Application of a Simulation Approach to Extremely Low Frequency Magnetic Field (ELF-MF) and Childhood Leukemia

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Epidemiology

by

Fan Zhao

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ABSTRACT OF THE THESIS

Investigating the Association Between Uncommon Exposures and Rare Disease Outcomes:

an Application of a Simulation Approach to

Extremely Low Frequency Magnetic Field (ELF-MF) and Childhood Leukemia

By

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Master of Science in Epidemiology

University of California, Los Angeles, 2020

Professor Leeka I. Kheifets, Chair

Background: Studying risk factors of rare outcomes can be difficult as single studies tend to have few exposed cases, resulting in rather wide confidence intervals. Therefore, combination of multiple studies is usually necessary to draw a conclusion. Pooling of individual patient data (IPD) is considered the gold standard due to increased statistical power through large sample sizes and other advantages. However, present pooling is limited to studies of the same designs, which does not make full use of existing data.

Objectives: To generalize pooling to studies of different designs (including cohort study, case control study, nested case control study and matched case control study), by incorporating

simulation of the association of extremely low frequency magnetic field (ELF-MF) and childhood leukemia.

Method: I first simulated large cohort and case control samples based on parameters extracted from both the literature and existing large cohort and case control datasets, which included ELF-MF exposure prevalence, childhood leukemia incidence rate, prevalence of confounders including age, gender, race and SES. Then I combined these simulated data using three different methods: two stage meta-analysis, one stage pooling and two stage meta-analysis with pooling.

Results: Estimates from three synthesis methods were close to the causal estimate and there was no obvious trend of overestimation or underestimation. One stage pooling seemed to have the worst efficiency with the widest 95%CI but the difference was not significant.

Conclusion: The performance of three synthesis methods in the study was not certain. Further simulations with varying parameters and possible mathematical derivations are needed to assess why and when these methods lead to different effect estimates.

Keywords: Individual patient data (IPD); meta-analysis; pooling; simulation with R; Extremely Low Frequency Magnetic Field (ELF-MF); childhood leukemia

The thesis of Fan Zhao is approved.

Catherine M. Crespi

Roch A. Nianogo

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University of California, Los Angeles

2020

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Investigating the Association Between Uncommon Exposures and Rare Disease Outcomes: an Application of a Simulation Approach to Extremely Low Frequency Magnetic Field (ELF-MF) and Childhood Leukemia

Introduction

Rare diseases are defined by the Rare Disease Act of 2002 as diseases affecting 200,000 individuals or fewer in the United States. (1) Research on treatments or management strategies for rare diseases can be challenging primarily due to the limited number of individuals who will be eligible to participate in any given study, resulting in underpowered studies. (2,3) Therefore, combination of multiple studies is usually necessary to draw a conclusion.

Traditional meta-analysis methods involve combining and analyzing aggregate data (usually obtained from published studies). (4) Pooling of individual participant data (IPD) has been considered the gold standard. (5) By standardization of data and analyses across studies, IPD removes potential sources of heterogeneity across studies and increases the statistical power and precision of estimates. (6–8)

However, studies of rare outcome tend to be of different designs. (9) A case-control design is often necessary for studies investigating rare outcomes. Other possibilities include nested case control designs, nested prospective studies and prospective cohort designs. (9,10) To combine information from these studies with disparate designs is necessary to make full use of existing IPD and several authors proposed generalized pooling methods. Brumback et al. proposed two stage meta-analysis with maximum likelihood estimations (MLE). (11) In the Hormonal Factors in Breast Cancer collaborative study, researchers have implemented Mantel-Haenszel stratified two stage meta-analysis. (12) Ahlbom et al. selected a control group from the Finland cohort study, making it into matched case control study, and then pooled with other 8 case control studies. (13)

In this project, we show the relative performance of these generalized pooling methods applied to studies of different designs (including cohort studies, case control studies, nested case control studies and matched case control studies), by incorporating simulation of the association of extremely low frequency magnetic field (ELF-MF) on childhood leukemia.

The investigation of the possible relation between magnetic field exposure and the occurrence of childhood cancer started with Wertheimer and Leeper's study. (14) Using wire codes, increased cancer occurrence was found to be associated with occupancy in higher exposure homes. Although not provided in the paper, calculated point estimates of odds ratio (OR) were consistently in the 2.0-3.0 range. However, this study has been criticized concerning exposure assessment, exposure misclassification by study investigators and absence of information on potential confounders such as maternal smoking or use of x-rays. (15) To address some of the shortcomings, others used field measurements, but these measurements were vulnerable to nonresponse bias. (16) The methods of subject identification and selection could also introduce bias. Controls tended to be more residentially stable compared with cases and the possibility that mobility patterns of cases are affected by the disease could bias the results in a manner that would not have been identifiable with the available data. (16) To address this, studies utilized calculated fields. (15,17,18)

Due to the combination of an uncommon high exposure and a rare disease outcome, as well as possible confounding, exposure misclassification and selection bias by social economic status (SES) and mobility, epidemiologic evidence linking ELF-MF exposure to childhood leukemia appeared inconsistent, before the following pooled analyses were conducted. Greenland et al. and Ahlbom et al. pooled the major epidemiological studies in 2000, and reported an increased childhood leukemia risk associated with ELF-MF exposure above 0.3 or 0.4 uT (OR=1.69, 95% CI 1.25-2.29; OR=2.00, 95% CI 1.27-3.13 respectively). (13,19) A pooled analysis of ELF-MF

and childhood leukemia studies published after 2000 had similar, albeit somewhat reduced risk (OR=1.44, CI 0.88-2.36 for above 0.3uT). (20)

Given that some 40 epidemiologic studies have examined the relationship of magnetic fields or its surrogates and childhood leukemia, little can be gained from further repetition of investigations of risks at moderate and low exposure levels, unless such studies can be designed to test specific hypotheses, such as selection bias or aspects of exposure not previously captured. (21,22) New approaches are needed to elucidate this consistent, but small risk. One such approach depends on the presence in some apartment buildings of indoor substations, adjacent to living areas. In some circumstances, the apartment immediately above (or next to) the substation can receive an elevated exposure from it. (23–28) Assembling a cohort of children who have lived in such buildings and comparing different apartments in the same building, which are expected to have similar socio-economic characteristics, may be a way of avoiding socioeconomic bias, and assessing exposure without requiring subject participation. The study, known as "TransExpo," will be feasible only as an international collaboration, because of the low prevalence of such exposure situations in any one country. (29) The attraction of TransExpo includes objective exposure assessment blind to case/controls status, avoidance of selection bias due to differential participation of cases and controls, some control of unidentified confounding, and subjects with high exposure. However, different designs are being used due to various limitations in the availability and quality of information in different countries.

Methods

Aim

The aim of this paper is to show the relative performance of one stage and two stage pooling of rare outcomes studies with different designs, based on the association of ELF-MF and childhood leukemia.

Simulation set up

I first simulated large cohort, nested case control and matched case control samples based on parameters extracted from both the literature and existing large cohort and case control datasets that included ELF-MF exposure and childhood leukemia incidence. To accommodate matched case control studies, I also included confounders as matching factors (for example, in some countries buildings with transformers in which cases lived are identified and controls are selected from the same buildings, i.e. matched on buildings). For the sake of simplicity, I only simulated a general confounding variable. I also assumed no measurement error and no selection bias.

For the three cohort studies, I set sample sizes to 100,000, 500,000 and 1,000,000 with the same ELF-MF prevalence but they varied due to randomness. Childhood leukemia incidence was 0.05% among children and the prevalence of the confounder was 5%. I assumed that these variables followed the Bernoulli distributions. The simulation settings are presented in Table 1, based on the causal structure DAG (Figure 1). In particular, the probability of being exposed to ELF-MF was specified as:

$$P_E = \frac{\exp(\gamma_0 + \gamma_C C)}{1 + \exp(\gamma_0 + \gamma_C C)} \quad (1)$$

Similarly, the probability of leukemia given the ELF-MF exposure and the confounder was specified as:

$$P_D = \frac{\exp(\beta_0+\beta_E E+\beta_C C)}{1+\exp(\beta_0+\beta_E E+\beta_C C)}$$, where exp (β_E) is interpreted as odds ratio (OR) (2)

Featuring studies of rare outcome and exposure, it was often when there were no exposed cases in the above cohort simulations. Therefore, instead of sampling and selecting from cohort studies to get nested case control and matched case control studies, which poses technical difficulties in data simulation, I manipulated the feature of case control studies that controls be representative of the total population in terms of exposure and covariates prevalence, and implemented the following simulation method.

For nested case control studies, I first simulated the control arm with the same model (1) as the cohort to get the confounder as well as exposure. Then I calculated the prevalence of exposure and confounder in the case arm based on the following relationship with OR:

$$OR = \exp(\beta_E) = \frac{logOdds_{case}}{logOdds_{control}} = \frac{\log[P_{E-case}/(1-P_{E-case})]}{\log[P_{E-control}/(1-P_{E-control})]} \quad (3)$$

I built 3 nested case control studies this way, with sample sizes of 1,000, 5,000 and 10,000, with equal numbers of cases and controls.

Similarly, I simulated the control arm of matched case control studies based on the same model (1) as the cohort. Then I implemented 1:1 exact matching based on the confounder and calculated the prevalence of exposure in the case arm based on the equation (3). I built 3 matched case control studies this way, with sample sizes of 1,000, 5,000 and 10,000.

All scenarios were simulated S=500 times. (Figure 2) And I repeated the above procedure with varying parameters for ELF-MF prevalence (1.5%, 3% and 5%) and OR (1.5, 3 and 5), resulting in 9 situations. I used statistical software R version 4.0.0 (the R Foundation for Statistical Computing, Vienna, Austria) to simulate and analyze our data.

Random deviations of simulated studies from the true effect

Due to the random error of sampling, the effect estimates of ELF-MF on childhood leukemia [$\widehat{OR} = \widehat{\exp(\beta_E)}$] from simulated studies may not be the same as the causal effect. Therefore, I also pooled the three cohort studies, nested case control and matched case control studies separately with mixed-effects logistic regression model to gauge the size of the random error.

Table 1 Overview of Simulation Settings.

	Scenarios
Cohort study	
Confounding factor (C)	Binary, C ~Bernoulli(p); prevalence (Pc)=0.05
ELF-MF (E)[a]	Binary, E ~Bernoulli(p); γ_C=1.10; γ_0 varies.
Leukemia (D)[b]	Binary, D ~Bernoulli(p); $\beta_E$varies; β_C=1.60; $\beta_0$varies.
Sample size (N)	100,000, 500,000 and 1,000,000
Nested case control study	
Confounding factor (C) in the control arm	Binary, C ~Bernoulli(p); prevalence (Pc)=0.05
ELF-MF (E)[a] in the control arm	Binary, E ~Bernoulli(p); γ_C=1.10; γ_0 varies.
ELF-MF (E)[c] in the case arm	Binary, E ~Bernoulli(p)
Sample size (N)	1,000, 5,000 and 10,000
Matched case control study	
Confounding factor (C) in the control arm	Binary, C ~Bernoulli(p); prevalence (Pc)=0.05
ELF-MF (E)[a] in the control arm	Binary, E ~Bernoulli(p); γ_C=1.10; γ_0 varies.
ELF-MF (E)[c] in the case arm	Binary, E ~Bernoulli(p)
Confounding factor (C) in the case arm	Binary, C ~Bernoulli(p); prevalence (Pc)=0.05 (the same as in the control arm).
Sample size (N)	1,000, 5,000 and 10,000
Number of simulations (S)	500

OR = odds ratio; NCC= nested case control study; MCC=matched case control study.

[a] $P(E) = \frac{\exp(\gamma_0+\gamma_C C)}{1+\exp(\gamma_0+\gamma_C C)}$, 1.5%, 3% and 5%.

[b] $P(D) = \frac{\exp(\beta_0+\beta_E E+\beta_C C)}{1+\exp(\beta_0+\beta_E E+\beta_C C)}$, exp ($\beta_E$)=1.5, 3 and 5.

[c] $\frac{P(E)}{1-P(E)}$ in the case arm is equal to $OR \times \frac{P(E)}{1-P(E)}$ in the control arm.

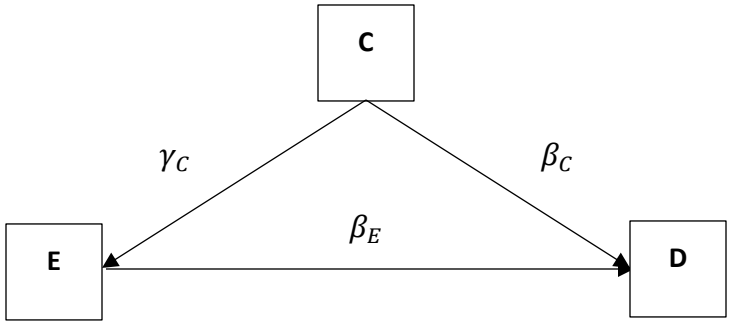

Figure 1 Causal diagram illustrating causal structures under investigation. Gamma coefficients for association of confounder (C) and ELF-MF (E) and beta coefficients for effects of ELF-MF (E) on childhood leukemia (D) in equations 1 and 2.

Methods for pooling analysis

Two stage meta-analysis

Effect estimates (ORs) were obtained for each study separately and then combined using a DerSimonian and Laird random-effects meta-analysis model. For this random-effects meta-analysis model, I assumed that the studies have enough in common that it made sense to synthesize the information, but there is no reason to assume that they are 'identical' in the sense that the true effect size is exactly the same in all the studies.

One stage pooling

I sampled from cohort studies to make nested case control studies. I then pooled, in which data from all studies were entered simultaneously into a single mixed-effects logistic regression model with random intercepts for study. I broke the matching and adjusted for the matching factor. In this case, I assumed that baseline risk is different between studies, but still assumed that relative risks are same across studies.

Two stage meta-analysis with pooling

I first pooled cohort studies, nested case control studies and matched case control studies separately, getting effect estimates for three types of studies and then combined them using a DerSimonian and Laird random-effects meta-analysis model.

Performance measures

I pooled nine studies with three methods and estimated the effect of ELF-MF on childhood leukemia [$\widehat{OR} = \widehat{\exp(\beta_E)}$]. I assessed the variability between estimates from 500 simulation runs (i.e. the variation between different studies) by 2.5 and 97.5 percentiles of the 500 OR estimates. I also took it as a measure of efficiency. Bias of different methods was defined as the difference between the mean of $\widehat{OR}$ estimates based on 500 simulation runs and the true exposure effect OR, calculated as percentage change $\left(\frac{\overline{\widehat{OR}}-OR}{OR}\right) \times 100\%$. A negative bias indicates that the method underestimates the true underlying effect, and a positive bias indicates that the method overestimates the true underlying effect. I also assessed precision in estimates with the empirical standard error in the log scale, that is, the standard deviation of the $\widehat{\beta_E}$ estimates across the samples, $\sqrt{\frac{1}{(S-1)}\sum_{h=1}^{S}(\hat{\beta}_h - \bar{\hat{\beta}})^2}$, where h is the *hth* simulation ranging from 1 to S and $\bar{\hat{\beta}}$ is the empirical mean $\widehat{\beta_E}$ of S simulations. The higher the SD, the higher the variability is and thus the lower the efficiency of the method is.

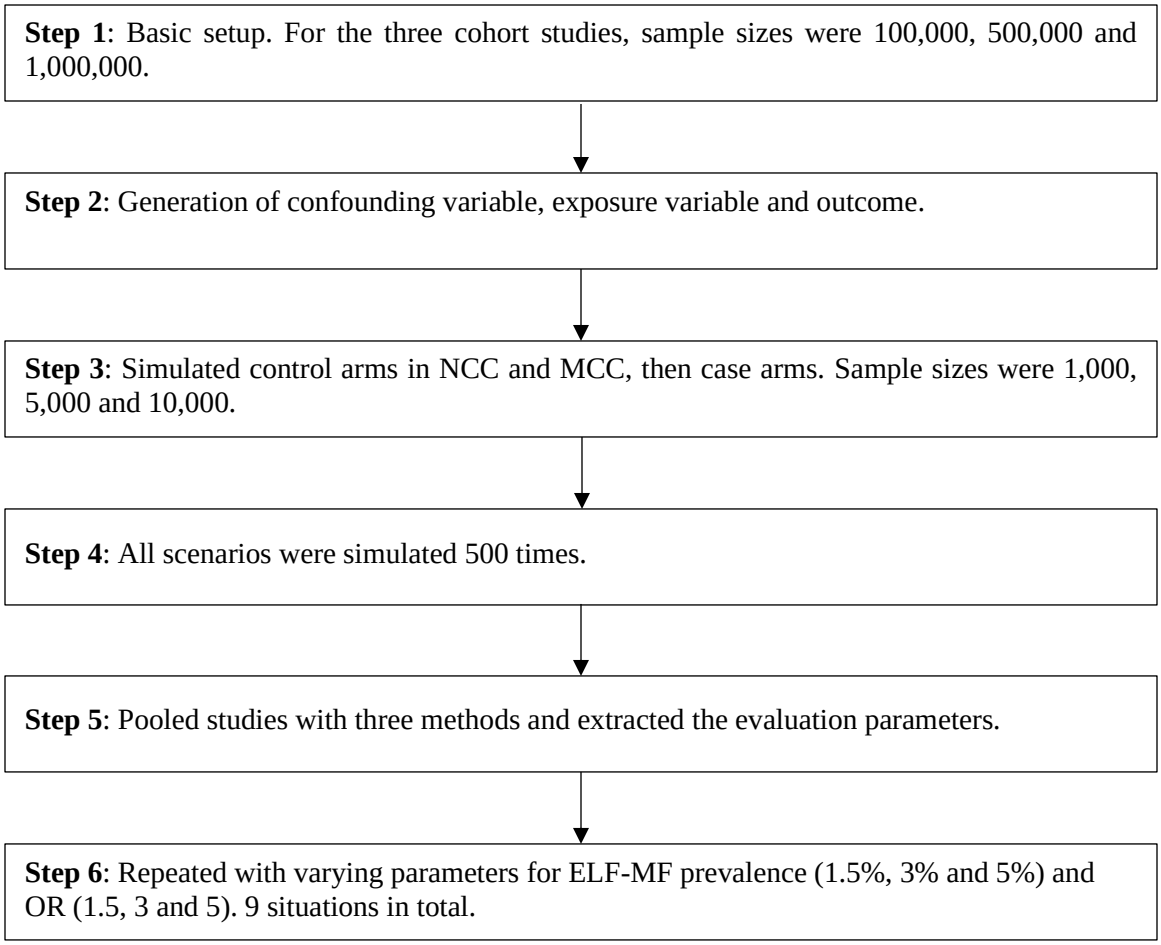

Figure 2 Simulation of the data and pooling. NCC: nested case control study; MCC: matched case control study.

Result

Pooled estimates from simulated cohorts, nested case controls and matched case controls were close to the causal estimates. (Figure 3, Appendix Table 1) Nested case control studies and matched case control studies were more efficient than cohort studies in that cohort studies had the widest 95%CI when the prevalence of exposure ELF-MF and OR were set. Measure by the width of 95%CI as well as standard error, the efficiency of nested case control studies and matched case control studies was similar. With the increase of exposure prevalence, efficiency improved in all

three study designs. On the contrary, with the decrease of OR to be closer to the null, efficiency improved in all three study designs.

Estimates from three synthesis methods were close to the causal estimate and there was no obvious trend of overestimation or underestimation. One stage pooling seemed to have the worst efficiency with the widest 95%CI but the difference was not significant. Similar with pooled estimates from original simulated studies, as exposure prevalence increased, efficiency improved in all three synthesis methods. In contrast, as OR decreased to be closer to the null, efficiency improved in all three synthesis methods. (Figure 4, Appendix Table 2 and 3)

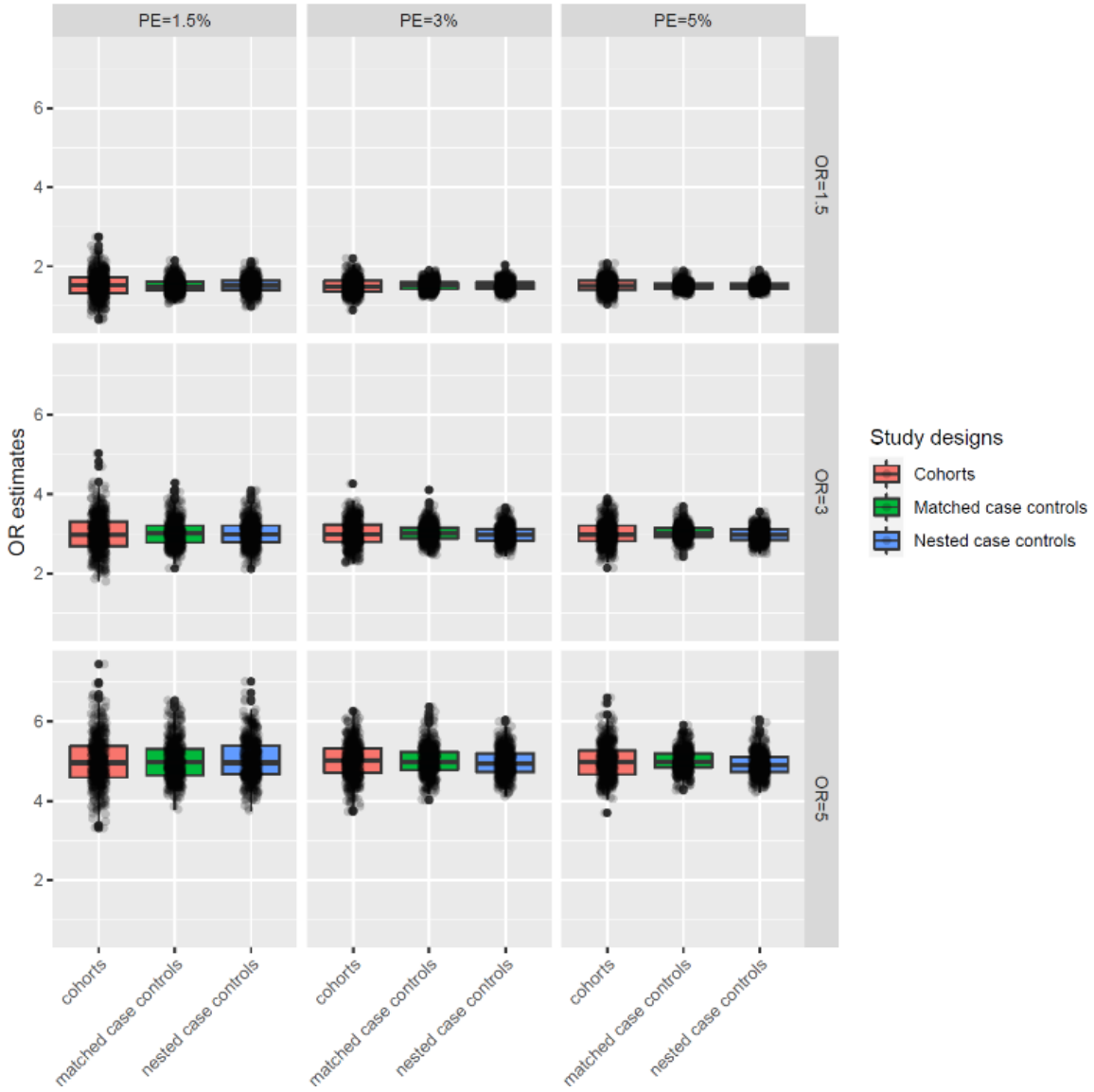

Figure 3 Pooled estimates from simulated cohorts, nested case controls and matched case controls, pooled with mixed-effects logistic regression model, with different combinations of ELF-MF prevalence (1.5%, 3% and 5%) and OR (1.5, 3 and 5). 9 situations in total.

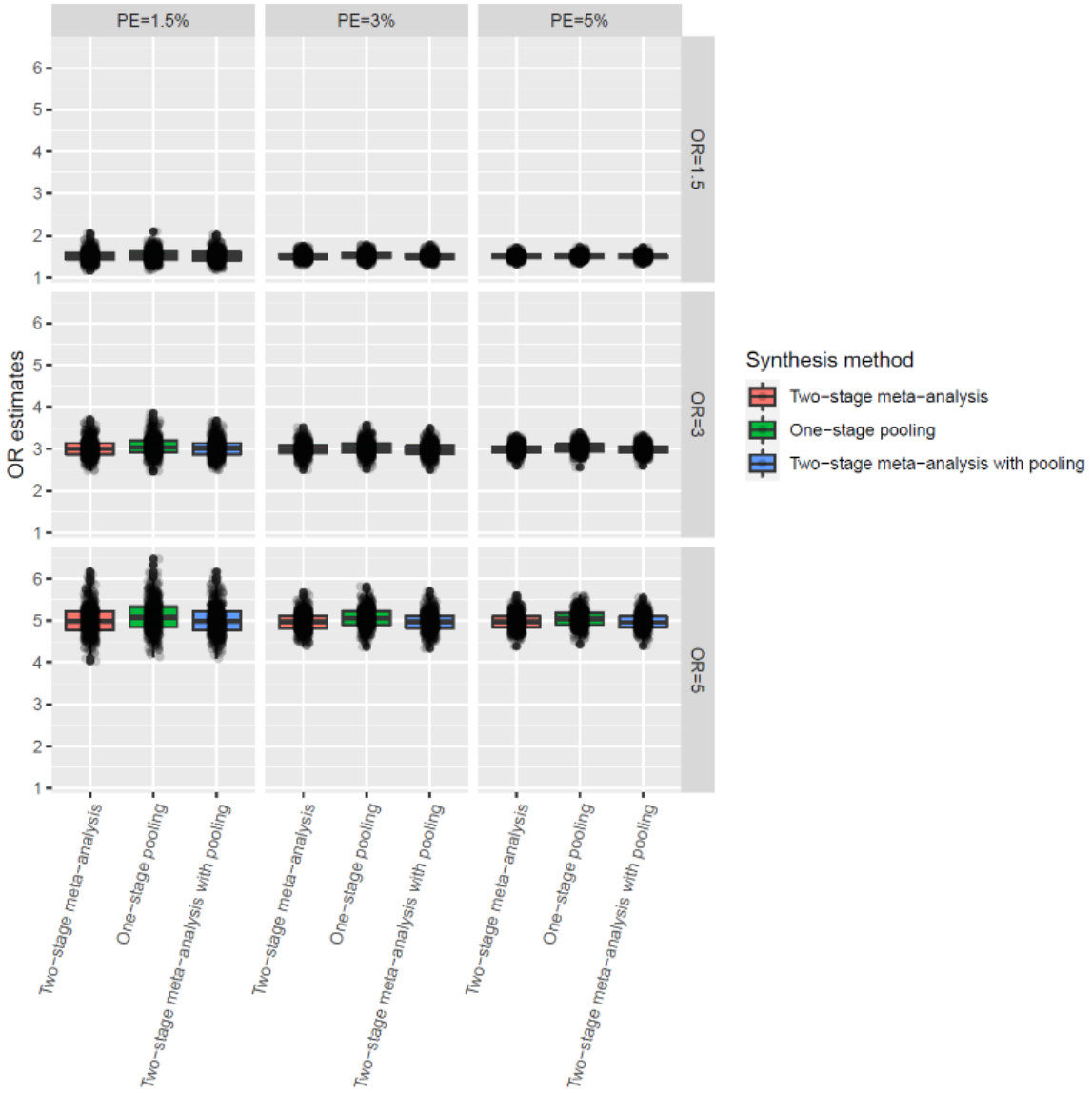

Figure 4 Estimates from three synthesis methods: two stage meta-analysis, one stage pooling and two stage meta-analysis with pooling, with different combinations of ELF-MF prevalence (1.5%, 3% and 5%) and OR (1.5, 3 and 5). 9 situations in total.

Discussion

The aim of this paper was to compare the relative performance of different methods to synthesize rare outcome studies of different designs. All three methods had similar point estimates, which were close to the causal estimate, but the one-stage pooling method where I first sampled

from cohort studies to make nested case control studies then pooled with mixed-effects logistic regression seemed to have the worst efficiency, measured by the widest 95%CI. But the difference was not significant and there was no essential difference among the three synthesis methods in terms of bias and precision.

There are two statistical approaches for conducting an IPD meta-analysis: one-stage and two-stage. The one-stage approach analyzes the IPD from all studies simultaneously, for example, in a hierarchical regression model with random effects. The two-stage approach derives aggregate data (such as effect estimates) in each study separately and then combines these in a traditional meta-analysis model. (8) My first and second method corresponded to the two-stage and one-stage meta-analysis. The two-stage approach is often preferred because in the second stage it uses standard meta-analysis methods that are well documented, for example, in the Cochrane Handbook. (30–32) In my study, two-stage meta-analysis performed better in the sense of higher precision, whether I obtained the first stage estimates directly or by pooling. However, one-stage methods have also been recommended because they use a more exact likelihood specification, which avoids the assumptions of within-study normality and known within-study variances, which are especially problematic in meta-analyses with small studies and/or rare events. (33,34) Yet, one-stage methods are also criticized for being computationally intensive and prone to convergence problems. (34,35)

Several authors have investigated the difference between one-stage and two-stage IPD meta-analysis results, either empirically, theoretically or via simulation. (31,32,34,36–39) Most authors conclude that they give very similar results. However, differences can arise, and sometimes these may even be large with discrepant statistical or clinical significance. (34,40) Most differences between one-stage and two-stage approaches occur because of different modelling assumptions, including the specification of the likelihood and included parameters, the choice of fixed or random

effects and the utilization of correlation. In my study, the best choice of model specification and/or estimation method are unclear, therefore I implemented both one-stage and two-stage analyses and compared their results to check whether conclusions are the same. (8) In my two-stage meta-analysis, I assumed that effect sizes in individual studies represent a random sample from a particular distribution of true effect. (41) The two-stage meta-analysis outperformed one-stage pooling in the sense of higher precision here. Further looking into the reasons is necessary.

To my knowledge this is the first paper seeking to generalize pooling methods with simulation. Simulation methods are relatively straightforward once the assumptions of a model and the parameters to be used for data generation are specified. (42)

There are several limitations of this simulation study that should be noted. First, due to hardware calculation capacity strains worsened by the rare exposure and outcome, I did not sample from cohorts to simulate nested case controls and matched case controls, which are the most common ways. Instead I utilized the quality that controls be representative of the total population in terms of exposure and covariates prevalence and simulated the control arms first. Then I simulated case arms based on the relationship with OR. Because this simulation method stuck to the qualities that were supposed to be achieved by nested case control and matched case control designs, I assumed this did not pose a big problem. And as was shown in Table 2 and Figure 3, pooled estimates from simulated cohorts, nested case controls and matched case controls centered around the causal estimates. Second, this study only simulated the simplest situation where there is only one binomial confounding variable but real-world data are much more complex and often do not adhere to the assumptions and parameters by which data are generated here. Therefore, I should further apply these pooling methods to real life data and compare results if possible. Third, it is practically impossible to know the values of true population parameters that are incorporated into current

simulation. For example, the regression coefficients $\hat{\beta}$ often may be unknown. Even if previous research provides empirically estimated parameter estimates, the exact value for these population parameters is still unknown due to sampling error. Also, in the study I set both the outcome and exposure to be rare (prevalence 0.05% and 1.5%-3% respectively), its generalization to study of other more common outcomes should be further studied. To deal with these, I can run simulations across a wider range of parameter values to understand how their models may perform under different conditions. Last, not all statistical questions require simulations to obtain meaningful answers. I cannot exclude the possibility that the pooling questions here can be answered through mathematical derivations. If that is the case, simulation studies can demonstrate only what was shown already to be true through mathematical proofs. (43)

Appendix

Table 1 Mean OR Estimates and 95%CI from Cohort, Nested Case Control and Matched Case Control Studies by Pooling.

$\widehat{\overline{OR}}(95\%\ CI)$[a]	OR=1.5	OR=3	OR=5
P(E)=1.5%	1.4920 (1.3154-1.7267) 1.5044 (1.3919-1.6362) 1.4965 (1.3916-1.6160)	2.9656 (2.6826-3.3049) 2.9884 (2.7801-3.1994) 2.9982 (2.7700-3.1997)	4.9640 (4.5901-5.3840) 5.0115 (4.6678-5.3949) 4.9968 (4.6448-5.3091)
P(E)=3%	1.4880 (1.3511-1.6298) 1.5022 (1.4209-1.5917) 1.5073 (1.4188-1.5920)	2.9884 (2.7883-3.2340) 2.9737 (2.8186-3.1163) 3.0097 (2.8697-3.1598)	4.9943 (4.7050-5.3295) 4.9523 (4.7241-5.2006) 4.9964 (4.7761-5.2350)
P(E)=5%	1.5021 (1.4006-1.6358) 1.4974 (1.4289-1.5656) 1.5028 (1.4356-1.5682)	2.9892 (2.8088-3.1998) 2.9652 (2.8308-3.1077) 3.0126 (2.9086-3.1284)	4.9786 (4.6626-5.2670) 4.9149 (4.7235-5.1083) 5.0113 (4.8412-5.2017)

In the cells are estimates of cohort studies, nested case control studies and matched case control studies in sequence.

[a]effect estimates of ELF-MF ≥0.4uT on incidence of childhood leukemia of three simulated types of studies: cohort, nested case control and matched case control studies measured by $OR = \exp(\beta_E)$. Studies were pooled with mixed-effects logistic regression model, respectively. 95%CI is calculated as 2.5 and 97.5 percentiles of the S=500 samples.

Table 2 Mean OR Estimates and 95% CI Yielded by Three Methods.

$\widehat{OR}$[a] (95% CI[b])	OR=1.5	OR=3	OR=5
P(E)=1.5%	1.5105 (1.4282-1.5978)	3.0106 (2.8701-3.1412)	4.9923 (4.7674-5.2142)
	1.5179 (1.4270-1.6171)	3.0543 (2.9159-3.2007)	5.0855 (4.8456-5.3259)
	1.5054 (1.4155-1.6000)	3.0074 (2.8621-3.1417)	4.9928 (4.7635-5.2137)
P(E)=3%	1.5052 (1.4485-1.5624)	2.9843(2.8966-3.0879)	4.9651 (4.8085-5.1184)
	1.5134 (1.4618-1.5752)	3.0197(2.9145-3.1274)	5.0517 (4.8948-5.2217)
	1.5011 (1.4451-1.5590)	2.9816(2.8799-3.0891)	4.9655 (4.8154-5.1248)
P(E)=5%	1.5001 (1.4575-1.5436)	2.9904 (2.9136-3.0708)	4.9709 (4.8402-5.0983)
	1.5084 (1.4633-1.5550)	3.0231 (2.9361-3.1087)	5.0420 (4.8986-5.1900)
	1.4973 (1.4550-1.5409)	2.9898 (2.9101-3.0696)	4.9709 (4.8339-5.0987)

In the cells are estimates of cohort studies, nested case control studies and matched case control studies in sequence.

[a]the mean of the estimated effect of ELF-MF ≥0.4uT on incidence of childhood leukemia across the S=500 simulated samples, measured by OR.

[b]2.5 and 97.5 percentiles of the S=500 samples.

Table 3 Efficiency and Bias Yielded by Three Methods.

SD[a] (Bias[b])	OR=1.5	OR=3	OR=5
P(E)=1.5%	0.0878 (-0.70%)	0.0686 (-0.35%)	0.0681 (0.15%)
	0.0914 (-1.19%)	0.0723 (-1.81%)	0.0729 (-1.71%)
	0.0904 (-0.36%)	0.0692 (-0.25%)	0.0669 (0.14%)
P(E)=3%	0.0469 (0.30%)	0.0511 (0.52%)	0.0451 (0.70%)
	0.0664 (-1.38%)	0.0537 (-0.66%)	0.0469 (-1.03%)
	0.0434 (0.30%)	0.0519 (0.61%)	0.0425 (0.69%)
P(E)=5%	0.0428 (-0.00%)	0.0405 (0.32%)	0.0384 (0.58%)
	0.0432 (-0.56%)	0.0417 (-0.77%)	0.0401 (-0.83%)
	0.0434 (0.18%)	0.0406 (0.34%)	0.0382 (0.58%)

In the cells are estimates of cohort studies, nested case control studies and matched case control studies in sequence.

[a]the standard deviation of the estimates across the S=500 samples.

[b]the bias as a percentage of effect of ELF-MF ≥0.4uT on incidence of childhood leukemia in simulations (OR=1.5, 3 and 5, respectively). Positive value means overestimates and negative means underestimates.

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