ARTICLE TYPE

Application of targeted maximum likelihood estimation in public health and epidemiological studies: a systematic review

Matthew J. Smith^{*1} | Rachael V. Phillips² | Miguel Angel Luque-Fernandez^{$\pm 1,3$} | Camille Maringe^{± 1}

¹Inequalities in Cancer Outcomes Network, London School of Hygiene and Tropical Medicine, London, England, United Kingdom

²Division of Biostatistics, School of Public Health, University of California at Berkeley, California, United States of America

³Department of Statistics and Operations Research, University of Granada, Granada, Spain

Correspondence

*Matthew J. Smith. Email: matt.smith@lshtm.ac.uk

Present Address

London School of Hygiene and Tropical Medicine, Keppel Street, London, England, United Kingdom, WC1E 7HT

[±] Both authors contributed equally to this work.

Abstract

Background The Targeted Maximum Likelihood Estimation (TMLE) statistical data analysis framework integrates machine learning, statistical theory, and statistical inference to provide a least biased, efficient and robust strategy for estimation and inference of a variety of statistical and causal parameters. We describe and evaluate the epidemiological applications that have benefited from recent methodological developments.

Methods We conducted a systematic literature review in PubMed for articles that applied any form of TMLE in observational studies. We summarised the epidemiological discipline, geographical location, expertise of the authors, and TMLE methods over time. We used the Roadmap of Targeted Learning and Causal Inference to extract key methodological aspects of the publications. We showcase the contributions to the literature of these TMLE results.

Results Of the 81 publications included, 25% originated from the University of California at Berkeley, where the framework was first developed by Professor Mark van der Laan. By the first half of 2022, 70% of the publications originated from outside the United States and explored up to 7 different epidemiological disciplines in 2021-22. Double-robustness, bias reduction and model misspecification were the main motivations that drew researchers towards the TMLE framework. Through time, a wide variety of methodological, tutorial and software-specific articles were cited, owing to the constant growth of methodological developments around TMLE. **Conclusions** There is a clear dissemination trend of the TMLE framework to various epidemiological disciplines and to increasing numbers of geographical areas. The availability of R packages, publications have contributed to an exponential increase in the number of studies that understood the benefits, and adoption, of TMLE.

KEYWORDS:

Targeted Maximum Likelihood Estimation (TMLE), Epidemiology, Observational Studies, Causal Inference, Systematic Review

1 | BACKGROUND

Public health decisions across many clinical specialities are often informed by research exploring the relationship between exposures and patient health outcomes. To ascertain a causal relationship, randomised control trials (RCT) are considered the gold standard because, through randomisation of subjects to a treatment, they reduce the possibility of bias. Observational data offer invaluable opportunities to study causal relationships in contexts where clinical trials might prove infeasible or unethical, as well as for studying groups of the population typically excluded from trials or beyond the initial target population. Under correct adjustment for selection bias, missingness, interference, and confounding, observational data complements the evidence coming from RCTs.

In both RCT and observational studies, a causal exposure-outcome relationship is presented with a causal estimand, such as the average treatment effect (ATE). Methodological statistical developments for causal inference attempt to produce the least biased estimate of the estimand and accurate inference. G-computation, Propensity Score (PS), and Inverse Probability of Treatment Weighting (IPTW) estimators rely on parametric modelling assumptions, which are susceptible to model misspecification (i.e., exclusion of the underlying and unknown data-generating distribution from the model, which can lead to biased estimates with small standard errors and thus misleading results). Double-robust methods, like Augmented Inverse Probability of Treatment Weighting (AIPTW) and Targeted Maximum Likelihood Estimation (TMLE), aim to minimise model misspecification by requiring estimation of both the outcome and exposure mechanisms. They provide a consistent estimator as long as either the outcome or exposure model is correctly specified. Double-robust methods often outperform single-robust methods in point and interval estimation.^{1,2}

TMLE, also known as targeted minimum loss-based estimation, was introduced by van der Laan and Rubin in 2006.³ In general, TMLE is a two-step process that involves (1) initial estimation of the outcome and intervention models, and then (2) in a "targeting" step, uses information from them to optimise the bias-variance trade-off for the target estimand (e.g., ATE), rather than the whole outcome probability distribution. Furthermore, to avoid model misspecification, ensemble machine learning algorithms are used to estimate the initial models. In particular, the Super Learner (SL) algorithm for stacked ensemble machine learning is most commonly used as it is theoretically grounded and proven to perform optimally in large samples.⁴

We lightly detail the technical steps involved in the TMLE of the ATE, i.e., the effect of a binary exposure A on a postexposure outcome Y, adjusted by baseline covariates W^{5} . The prediction function for the mean outcome Y, given exposure A and covariates W is estimated, most commonly, using SL. We could use this estimated prediction function, $\hat{E}[Y|A, W]$, to arrive at an estimate of the ATE. Specifically, we would obtain predicted outcomes under a counterfactual scenario where all subjects receive the exposure/treatment versus another scenario where no one receives it. The average difference between these predicted counterfactual outcomes is an estimate of the ATE. However, formal statistical inference (i.e., confidence intervals and p-values) cannot be obtained for this estimate and it is susceptible to residual confounding; the latter can be reduced by using the information on how each individual was assigned or allocated to each level of the exposure. We, therefore, estimate the function for predicting the probability of being exposed, given the covariates W, using SL (exposure model, i.e. propensity score). These first steps are common to other double-robust estimators of the ATE, such as AIPTW. We then calculate the so-called "clever covariate" for the ATE, which is the individual values of the binary exposure weighted by the predicted probabilities of the exposure, given W. This is similar to IPTW, except here we weight the predicted probability of each exposure level instead of the outcome. The fluctuation parameter (ϵ) describes the difference between the observed outcome Y and the initial predictions of the outcome from the outcome model. It is calculated through maximum likelihood estimation (MLE) by regressing the clever covariate on the observed outcome and incorporating as offset the predicted outcome values. When the fluctuation parameter is estimated as close to 0 there is little difference between the observed and predicted outcomes; thus, the propensity score does not provide additional information for the initial estimate of the outcome model because it was correctly specified. If the fluctuation parameter is not close to 0, then this indicates the presence of residual confounding in the initial estimate. The initial outcome model's predictions for each level of the binary exposure are updated using the fluctuation parameter ϵ as a weight, and the final ATE estimate is calculated from these updated estimates. The functional delta method based on the influence function can be used to derive the standard error of the ATE and construct Wald-type confidence intervals.

Since 2006, the TMLE framework has experienced a growing number of theoretical and applied developments, and it has expanded further after a book that shared the TMLE framework to the international community of applied researchers was published in 2011.² Targeting specifically applied researchers, efforts were made to provide lay-language descriptions of the framework and exemplify its applications.^{5–7} Furthermore, in 2018, a second book was published disseminating more advanced applications of the TMLE framework to data scientists with a particular focus on longitudinal settings.⁸ TMLE is a robust framework for statistical analysis in clinical, observational and randomised studies. Since 2016, the American Causal Inference Conference has hosted a data challenge in which teams compete to estimate a causal effect in simulated data sets based on real-world data, such as from healthcare or education.⁹ The competition is a proving ground for cutting-edge causal inference methods that have the potential to transform program evaluation. TMLE has consistently been a top-performing method.¹⁰

The use of robust statistical methods is key to obtaining reliable results for public health and epidemiological research and maximising their benefit to society. Evidence shows that TMLE, by blending flexible machine learning methods and causal inference principles, is one such step towards robust causal claims that bear significant and practical effects. We reviewed the literature around public health and epidemiological applications of TMLE to date, alongside key TMLE developments over the last 20 years. We highlight the speed at which the field developed and spread through the scientific community, and identify areas for further development to increase the utility of the TMLE framework in epidemiological and applied research.

2 | METHODS

Protocol registration and reporting standards

This study is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We registered this systematic review with PROSPERO (ID: CRD42022328482).

Information sources

We searched the PubMed medical literature database for published epidemiological studies using TMLE in any epidemiological field (i.e., observational settings in biomedical sciences, including clinical epidemiology and public health). We searched for publications from any time up to 20th May 2022, the date the search was executed. The search strategy comprised of two specific groups of search terms focusing on TMLE and epidemiology. Relevant Mesh headings were included as were free-text terms, searched in the title, abstract or keyword fields. We used general and specific TMLE search terms, such as "targeted maximum likelihood estimation", "targeted minimum loss-based estimation", and "targeted machine learning". Epidemiological search terms included "epidemiology", "public health", "population", or "treatment". The two specific groups of terms were combined with 'AND' to retrieve the final set of results. Search strategies were developed with an information specialist (MALF). The full search strategy is shown in Table 1.

TABLE 1 Boolean search queries

Query	Boolean terms	Results
#1	(epidemiology OR (public AND health) OR population OR treat*)	11,004,506
#2	("targeted maximum likelihood estimation") OR ("targeted minimum loss based estimation") OR ("targeted minimum loss-based estimation") OR ("TMLE") OR ("targeted machine learning") OR ("targeted learning") OR ("targeted machine-learning")	311
#3	#1 AND #2	226

Eligibility criteria

We excluded studies that did not report the use of TMLE as a tool to explore their (possibly causal) estimand of interest. We also excluded experimental studies, such as RCTs (n=15). We did not consider manuscripts that compared the performance of TMLE to other estimators, when there was no new development proposed and even if there was an applied question of interest, such as in Luque-Fernandez et al.¹¹ Studies were restricted to the English language and primary research studies. Secondary research studies, such as reviews and comments of TMLE, conference abstracts and brief reports, and preprints were not searched. We classified the retained manuscripts into observational, methodological and tutorial articles. TMLE methodological development articles and tutorials were considered separately, even if they contained a methodological development specifically designed to investigate an epidemiological question within the same article. We make reference to these methodological articles throughout this review, as they underpin the applied publications.

Study selection, data extraction and management

All retrieved publications were imported into the Endnote reference software where they were checked for duplication. Two of the three lead researchers (authors MJS, MALF and CM) were randomly allocated two-thirds of the 226 articles, to screen titles and abstracts of each publication independently and classify these into (1) observational, (2) methodological developments, (3) tutorial, (4) systematic review, (5) RCT, or (6) not relevant (Figure 1). Disagreements were discussed and adjudicated by the third independent reviewer, where necessary. Two researchers (authors MJS and CM) independently reviewed the full text of all eligible observational publications for data extraction.



FIGURE 1 Flow diagram of studies included in the systematic review

3 | RESULTS

We found 226 unique publications published prior to 20th May 2022 in PubMed (Figure 1). Of these, 95 articles were a methodological development (including theoretical - or software-based), eight were tutorials, five were systematic reviews, and fifteen were RCTs. Of the 22 articles that were not relevant, three mentioned "TMLE" only in the author fields, one was a discussion of currently existing methods, twelve were assessments of *learning* (educational) programs that are *targeted* towards clinical environments, and six were comparisons of machine learning algorithms to other prediction models (without mention of TMLE). Overall, we focused on 81 observational studies in this systematic review for which full texts were available; six publications were not open-access and full texts were obtained from the corresponding authors.

3.1 | Dissemination and uptake of the TMLE framework

There has been a growing uptake of the TMLE framework over time, with five or fewer applied publications per year until 2017, and up to 21 in 2021. The majority (58, 71.6%) of publications using TMLE were published in the last three and a half years, starting in 2019. Most studies (77, 95.1%) cited the authors of particular TMLE methods they apply, whereas four (4.9%) did not cite any TMLE references. The large majority of these first epidemiological studies benefit from the expert knowledge of an author who is (or was) part of Professor Mark van der Laan's lab. (Table 2)

Of the 81 studies included, two-thirds were conducted in the United States of America (US) (53, 65.4%, Figure 2), $^{12-64}$ with 100% of articles before 2017 being published in the US and down to 50% of all 2021 articles. Publications from Europe or Scandinavia (10, 12.3%), $^{65-74}$ Africa (4, 4.9%), $^{75-78}$ Middle East (5, 6.2%), $^{79-83}$ and Oceania or Asia (8, 9.9%) $^{84-91}$ represent between 20% (in 2017) and 70% (in 2022, up to May 2022) of all applied studies published in the last 6 years. (Figure 2, Table 2) In the US, the majority of publications (28) were from California, including 20 from the University of California at Berkeley, where TMLE was first described.

In the early years, the first authors tended to be qualitative academic experts, but we saw more variety in expertise and a larger number of practising clinicians leading observational studies in many epidemiological and public health fields in recent publications. The most common epidemiological sub-discipline was non-communicable disease (23, 28.4%), ^{16,27,31,32,34,36,38,47,52,55,60,62,63,65,70,71,73,78–82,87} followed by behavioural epidemiology (17, 21.0%), ^{14,21,28,40,43–45,48,49,53,54,58,59,67,84,89,90} and then infectious disease epidemiology (12, 14.8%). ^{17,24,46,50,51,69,74,76,77,83,88,92} Through time we see an uptake of TMLE in many more disciplines, such as pharmaco-epidemiology, ^{26,61,72,75} policy, ^{23,25,30,41,56,64,91} biomarker epidemiology, ^{12,13,19,20,22,42,85,86} environmental epidemiology, ^{15,29,35,39,57,66,68} occupational epidemiology, ^{18,33} and health economy.³⁷

We also studied the evolution of citations. When only methodological overviews of the TMLE framework were available, these were cited despite their heavy statistical requisite. Since 2016, tutorials were published and started to be cited alongside references for statistical packages. $^{1,5-7,93-96}$ (Table 2)

design 13,14,17-19,25-27,30,32,33,36,38-41,43,46,49,50,52,55,58-61,63,69,70,73-75,77,78,84-91 Cohort study was the (42, most prevalent design 51.9%), followed by cross-sectional (32,39.5%) (Appendix Table 2), 12,15,16,21-24,28,29,31,34,35,37,42,44,45,47,48,51,53,54,56,62,65-68,71,72,76,79,81 Other types of epidemiological design included casecontrol^{20,80,82,83,92} and ecological.^{57,64}

Many articles reported results from other statistical methods, in addition to reporting those obtained from TMLE. Over one-quarter of the studies used adjusted parametric regression (24, 29.6%), ^{15–17,23,26,31,33,36,38,42,44,50,55,67,68,71–73,77–79,83,87,92} one sixth (12, 14.8%) used IPTW, ^{14,17,29,34,43,53,54,57,59,61,75,76} one (1.2%) used AIPTW, ⁵⁶ three (3.7%) used non-parametric methods (e.g. Kaplan Meier), ^{17,33,55} and seven (8.6%) used unadjusted regression. ^{43,48,52,63,64} Some studies included more than one comparative method.

flexible estimation SuperLearner (SL) provides а machine learning approach to the of the initial outcome and intervention models. Of the 81 articles, more than half (47, 58.0%) SL used the

algorithm, $^{23,25,27,29-32,34,38,40-43,45-47,49-52,54-57,59,61-64,66,67,69,71,72,74,76,77,81-92}$ 18 (22.2%) used logistic regression, $^{12-18,21,26,28,33,35,36,44,53,75,80}$ and 16 (19.8%) did not specify the approach for the estimation of either the outcome or intervention model. 19,20,22,24,37,39,48,58,60,65,68,70,73,78,79 The average number of machine-learning algorithms considered by the SL was 6.3 (range 1 - 16), 19 different machine-learning algorithms were used across the articles (a machine-learning algorithm is a wrapper included within the SuperLearner² library in R software).

Variance of point estimates obtained from TMLE were estimated using the influence function (n=19, 23.5%), $^{15-18,20,23,28,36,51,64,65,71,72,79-83,87}$ bootstrap (n=6, 7.4%), 13,14,26,29,34,53 and Wald tests (n=2, 2.5%), 21,25 while 54 (66.7%) studies did not specify how standard errors were obtained. $^{12,19,22,24,27,31-33,35,37-50,52,54-63,66-70,73-78,84-86,88-92,97}$

The Causal Inference Roadmap⁹⁸ contains seven recommended criteria to define a causal effect: (i) specify the scientific question, (ii) specify the causal model, (iii) define the target causal quantity, (iv) link the observed data to the causal model, (v) assess identifiability assumptions, (vi) estimate the target statistical parameters, and (vii) interpretation of the results. On average, 5.3 (SD 1.0) criteria were complete per article. We considered a version of the Targeted Learning Roadmap⁹⁹ that contains five criteria: (i) specify the observed data and describe the data-generating experiment, (ii) specify a statistical model representing a set of realistic assumptions about the underlying true probability distribution of the data, (iii) define a target estimand of the data distribution that "best" approximates the answer to the scientific question of interest, (iv) given statistical model and target estimand, construct an optimal plug-in estimator of the target estimand of the observed data distribution, while respecting the model, and (v) construct a confidence interval by estimating the sampling distribution of the estimator. When the scientific question of interest is causal, step (iii) of the Targeted Learning Roadmap incorporates steps (ii)–(v) of the Causal Inference Roadmap.⁹⁹ On average, 3.3 (SD 1.0) criteria were complete per article. Most studies have room to state the necessary content for at least one more criteria.

Most publications (77, 95.1%) used R software to perform TMLE, ^{14–21,23–34,36–49,51,52,54–58,63–67,69–77,79–86,90–92} except four that used STATA. ^{62,68,78,87} Nonetheless, nine articles reported using another software tool (i.e., Stata/SAS/SPSS) alongside R for TMLE. ^{14,31,37,45,63,72,75,77,82} The most commonly used R software packages were *tmle*¹⁰⁰ (40, 49.4%) and *ltmle*¹⁰¹ (16, 19.8%).

3.2 | Showcase of the TMLE framework in different disciplines

In all disciplines and applications, applying the TMLE framework to their specific research question encouraged authors to review the strengths and limitations of their data and carefully consider how their data and setting might violate identifiability assumptions, which are assumptions necessary for causal inference but not TMLE. If, and only if, the identifiability assumptions are assumed to hold, the estimated effect is a causal effect. However, for observational studies, it cannot be known whether identifiability assumptions hold. Therefore, if an estimate is interpreted as a causal effect, then this interpretation should be accompanied by a discussion of the plausibility of identifiability assumptions. All disciplines and disease areas highlight issues with missing data and measurement errors and incorporate subject-matter knowledge. (Appendix Table 2) Model misspecification, which might result from imposing constraints that are unrealistic or not informed by subject-matter knowledge, was the first and foremost driver for using the TMLE framework. Three-quarters of the studies (n=68, 84.0%) provided at least one justification for using TMLE compared to another method. (Table 2) Standard regression techniques in settings with low incidence,²⁴ rare outcomes⁷⁵ or low sample size^{53,67} may over-fit the data or not converge: careful SL specifications overcome these limitations.^{24,37} Least biased and double-robust estimation were also widely cited advantages of the framework. These mean (i) the estimated parameter will be closest to the true value of our quantity of interest, even when our sample size is low, and (ii) only one of our initial models needs to be correctly specified.

There was a range of disease areas covered in the 23 **noncommunicable disease epidemiology** studies. The appealing property of TMLE was that it is a semiparametric estimator, allowing the use of machine learning algorithms to minimise model misspecification. ^{34,47,60,62,73,78,81,87} Additionally, extensions of TMLE have developed ways to appropriately handle the dual nature of time-varying confounding, which have been utilised in longitudinal studies analysing data on depression, ³² survival from acute respiratory distress syndrome, ⁵⁵ caries arising from intake of soda, ³⁶ effects of smoking on rheumatoid arthritis, ³⁸ and effects of asthma medication on asthma symptoms. ⁷⁰ Improved predictive performance ⁶⁵ and adjusting for informative censoring ⁵⁵ were additional reasons for using TMLE. Furthermore, the extension of TMLE to case-control studies, in which

sampling is biased with respect to the disease status, provided a platform for analysing the causal effect of reproductive factors on breast cancer by using case-control weighted TMLE.⁸²

In **infectious disease epidemiology** (IDE) articles, most were concerned with having a flexible modelling approach that does not impose assumptions on the functional form of the exposure-outcome relationship.^{46,51,69,76,88,92} A key feature of the IDE subdiscipline is that baseline confounders and exposures may change over time and can obscure the causal effect of interest.¹⁷ Standard survival modelling assumes that censoring and survival processes are independent, which is likely violated in this setting, and it assumes there is no time-dependent confounding.¹⁷ TMLEs with a working marginal structural model and for time-to-event outcomes permit evaluation of the effect of an exposure at multiple time points, which is beneficial when the interpretation of causal effects from hazard models is often difficult.¹⁰² Other studies have overcome this issue by using TMLE in a target trial framework or case-cohort studies.^{50,83}

In **behavioural epidemiology** manuscripts, the behavioural nature of the topics covered implied that RCTs are mostly unethical, bear prohibitive costs or have very small sample sizes. There are several key challenges for using observational data to study the causal effects of childhood adversities, ^{21,28} physical activity, ^{14,43,90} alcohol consumption⁴⁵ or supply⁸⁴ on various outcomes, including fractures, ¹⁴ mental health, ^{21,58,59} asthma, ⁶⁷ and pregnancy outcomes. ^{43,44} They include a risk for reverse causation; ^{55,58,59} high dimensional data and in particular, multidimensional exposures; ^{21,28} and measurement error resulting from self-reported exposures or outcomes. ^{44,59,89,90} Longitudinal relationships and time-varying confounding, where confounders of the effect of an exposure on an outcome can themselves be affected by prior exposures, as well as sample attrition, ^{40,84,89,90} are particular challenges faced by survey data that are collected in consecutive waves. ^{40,54,59,84,89,90} TMLE adjusts for time-varying confounders affected by prior exposure and employs a doubly robust estimation approach that allows for flexible model fitting. Additionally, as pointed out in 2016 by Ahern et al.,²¹ "TMLE with machine learning addresses the challenge of a multidimensional exposure because it facilitates 'learning' from the data the strength of the relations between each adversity [dimensions of the exposure] and outcome, incorporating any interactions or nonlinearity, specific to each [sub-group]".

The field of **biomarker epidemiology** is driven by the search for sets of candidate biomarkers that are important in determining given outcomes. Ranking the contributions of these candidate biomarkers is also of interest. Some studies used TMLE to measure variable importance in biomarker research^{12,20,86} and in other fields.⁶⁵ Dimension reduction for the estimation of causal effects is an aim in some biomarker examples.^{22,42,85} In the models presented in the publications, there are complex joint effects to consider in large correlated data, as well as longitudinal patterns and time-dependent confounding.^{22,42,85} Furthermore, two manuscripts present covariate selection algorithms ahead of causal effect estimation.^{85,86}

Research published in **environmental epidemiology** highlights challenges around the clear definitions of exposure and outcomes, ¹⁵ as there are likely many proxy and surrogate measures of exposure, ⁶⁶ coupled with potential exposure misclassification and measurement errors. ^{15,35} Nonetheless, TMLE was successfully applied to determine either causal attributable risk, ^{15,66} or risk differences. ²⁹

The only observational study of TMLE in **health economics** explored the relationship between financial resources leading to food insecurity and healthcare expenditure in a pay-to-access healthcare system. It uses ecological measures of exposure and outcome and leads to evidence for policy.³⁷

Two publications focused on **occupational epidemiology**.^{18,33} A key aspect of occupational epidemiology is accounting for the healthy worker survivor effect: a bias arising due to healthier workers accruing more exposure over time. These studies looked at exposure to particulate matter from aluminium or metalworking fluids in metal factory workers, which varied depending on the length of employment. Both studies benefited from TMLE's flexibility to allow for time-varying confounding of the exposure.

The field of **pharmacoepidemiology** is concerned with assessing treatment's efficacy in real-world settings and monitoring long-term side effects of treatments. Both objectives would be either impractical or too costly to study in RCTs, given the limited follow-up time available in clinical trials. TMLE has been used in this setting, as it provides a robust procedure for estimation.^{26,61,72,75} In particular, the flexibility of TMLE, provided through the specification of a diverse and rich set of machine

learning algorithms in the SL, is crucial for appropriately adjusting for confounding in observational studies.¹⁰³

Policy epidemiology assesses the effects of population programs or mandates. Lack of randomisation, such as in studies examining the association between speciality probation and public safety outcomes, ^{25,30} leads to an imbalance in the covariate distribution by exposure levels. Studies of cost-effectiveness may involve dealing with outliers which can be addressed with TMLE. ^{30,56} Other challenges include zero-inflation, such as the assessment of the effect of primary care physician density on arthroplasty outcomes, in which some areas had zero density. ⁵⁶ This is dealt with by using a mixture of models to assess the probability of non-exposure (i.e., very low density). ⁵⁶ Other policy studies presented challenges around missing data, ⁵⁶ reliance on epidemic modelling assumptions, ⁶⁴ target trial emulation, ⁹¹ or infeasible randomisation process. ⁴¹



FIGURE 2 World map of publications using targeted maximum likelihood estimation by the geographical location of the first author (2006 to mid-2022). Colours represent the number of observational studies and the crosshatch pattern identifies where at least one methodological publication stem from.

TABLE 2 Distribution of observational papers by year of publication and selected characteristics

												Ye	ear of pu	ıblica	ation													
		2009	2010		2011		2012		2013	2	2014		2015		2016	2	2017		2018	2	2019	2	2020	2	021	20)22 *	Total
	N	(%)	N (%)	Ν	(%)	Ν	(%)	Ν	(%)	Ν	(%)	Ν	(%)	Ν	(%)	Ν	(%)	Ν	(%)	N	(%)	Ν	(%)	Ν	(%)	Ν	(%)	N
Publications	2			1		1		1		2		1		5		4		6		12		16		21		9		81
TMLE expert (author) [±]	2	(100)		1	(100)	1	(100)	1	(100)	1	(50)	1	(100)	3	(60)	1	(25)	4	(67)	6	(50)	6	(38)	5	(24)	1	(11)	33
USA-based publication	2	(100)		1	(100)	1	(100)			2	(100)	1	(100)	5	(100)	3	(75)	6	(100)	9	(75)	10	(63)	11	(52)	2	(22)	52
Discipline																												
Behavioural epi				1	(100)									1	(20)			1	(17)	2	(17)	6	(38)	4	(19)	2	(22)	17
Biomarker	2	(100)												3	(60)							1	(6)	2	(10)			8
Environmental epi						1	(100)									1	(25)	1	(17)	3	(25)			1	(5)			7
Health economy											(50)						(0.5)			1	(8)		(2.5)		(10)			1
Infectious disease								-1	(100)	1	(50)					1	(25)	2	(50)	1	(8)	4	(25)	2	(10)	3	(33)	12
Non-Communicable Disease								1	(100)	1	(50)	1	(100)					3	(50)	3	(25)	4	(25)	9	(43)	2	(22)	23
Pharmaco-eni												1	(100)			1	(25)			1	(0)	1	(6)	2	(10)			2 4
Policy														1	(20)	1	(25)	1	(17)	1	(8)		(0)	1	(10)	2	(22)	7
101109														-	(20)	-	(20)	-	(17)	-	(0)			-	(5)	-	()	
Motivations [†]																												
Bias	1	(50)								2	(100)	1	(100)	1	(20)	1	(25)	2	(33)	5	(42)	5	(31)	12	(57)	6	(67)	36
Double-robust	1	(50)												1	(20)	1	(25)	2	(33)	2	(17)	5	(31)	6	(29)	4	(44)	22
Efficient																				2	(17)	5	(31)	2	(10)	3	(33)	12
Finite sample						1	(100)							_										2	(10)			3
Model misspecification	1	(50)		1	(100)	1	(100)							3	(60)	1	(25)	2	(33)	1	(8)	3	(17)	1	(57)	2	(22)	16
Positivity assumption																		1	(17)	1	(8)	1	(6)					3
Power None specified								1	(100)					1	(20)	2	(50)			5	(42)	1	(0)	2	(10)	1	(11)	16
None specified								1	(100)					1	(20)	4	(30)			5	(42)	4	(23)	2	(10)	1	(11)	10
Expertise first author																												
Biostatistician	1	(50)								1	(50)	1	(100)			1	(25)	2	(33)	2	(17)	2	(13)	4	(19)	2	(22)	16
Epidemiologist				1	(100)	1	(100)			1	(50)			3	(60)			1	(17)	4	(33)	6	(38)	7	(33)	1	(11)	25
MD														1	(20)	2	(50)			1	(8)	1	(6)	5	(24)	2	(22)	12
MD, MPH																				1	(8)	1	(6)					2
MD, PhD								1	(100)											3	(25)	2	(13)	3	(14)	3	(33)	12
Other																						2	(13)	2	(10)			4
PhD Not known	I	(50)												1	(20)	1	(25)	2	(33)	1	(9)	1	(6)			1	(11)	5
Ινοι κποwn														1	(20)			1	(17)	1	(8)	1	(6)			1	(11)	5
Citations 🖸																												
Overall TMLE method.	2	(100)		1	(50)	1	(100)			5	(56)	1	(33)	4	(33)	4	(50)	3	(33)	6	(19)	13	(42)	20	(38)	4	(16)	64
Specific TMLE method.				1	(50)			1	(100)	4	(44)	1	(33)	6	(50)	1	(13)	3	(33)	15	(47)	7	(23)	13	(25)	8	(32)	60
Tutorial																		1	(11)	7	(22)	7	(23)	14	(27)	7	(28)	36
R software												1	(33)	2	(17)	3	(38)	2	(22)	4	(13)	4	(13)	5	(10)	6	(24)	27
* Up to 20th May 2022																												

[±] TMLE expert is a current or past member of M.J. van der Laan's Lab.

[†] Proportions calculated over the number of publications within that year.

□ Proportions calculated over the total number of citations within that year.

3.3 | Methodological developments and their implementation

Over the years since the TMLE framework was first laid out,³ many contributions have been made to expand the settings in which TMLE is used, provide tools for implementation in standard software, and describe the TMLE framework and application in lay language. Thanks to this, the community of public health researchers and epidemiologists have started implementing the TMLE framework and its latest developments to obtain double robust, least biased and efficient estimates and statistical inference from studies. The properties of TMLE, in contrast to other estimators commonly used for causal inference, include that it is loss-based, well-defined, unbiased, efficient and can be used as a substitution estimator.

Figure 3 shows schematically when and why extensions of TMLE have happened in the last 15 years, as well as extensions and uptake. The 81 applied epidemiological studies are classified by methodological development used during the study. Appendix Table 1 provides further details regarding the methodological development references between 2006 and mid-2022 that are highlighted in Figure 3.

TMLE's superior efficiency and power are evidenced in small sample size settings where marginal effects from logistic regression models adjusted for (possibly many) covariates would not be recommended.¹⁰⁴ The implementation of TMLE in complex causal effect estimation problems is discussed in many publications, such as in settings with multiple time point interventions, ^{105,106} longitudinal data, ^{107,108} post-intervention effect modifiers, ¹⁰⁹ dependence of the treatment assignment between units ¹¹⁰ or censoring, ¹¹¹ causally connected units, ^{112,113} hierarchical data structures, ¹¹⁴ randomisation at the cluster level, ¹¹⁵ large electronic health record data, ¹¹⁶ and in meta-analyses. ^{117,118}

The TMLE framework is extended and discussed in the setting of case-control studies. One study matched cases to controls,¹¹⁹ another used two-stage sampling and nested case-control design.¹²⁰ Other studies required the design to be adaptive to possibly invalid assumptions of independent units¹²¹ or if the sample population differs from the (possibly ill-defined) target population.¹²²

The collaborative TMLE (C-TMLE), introduced in 2010,¹²³ is an extension of TMLE, in which information on the causal parameter of interest is used when estimating and selecting initial model(s). C-TMLE aims to improve the robustness and efficiency of the TMLE. Schnitzer *et al.*¹¹¹ highlight the pitfalls and their consequences of automated variable selection in causal inference, such as in the propensity score model, and how C-TMLE corrects for this. C-TMLE was later extended to measure variable importance¹²⁴ and to longitudinal data settings.¹²⁵ Proposals to enhance the C-TMLE algorithm include ordering covariates to decrease C-TMLE time complexity,¹²⁶ using LASSO with C-TMLE for the estimation of the propensity scores, ¹²⁷ and adaptive truncation of the propensity scores with C-TMLE to ensure positivity.¹²⁸

The pooled TMLE¹²⁹ was developed for the context of longitudinal data structures with baseline covariates, time-dependent intervention nodes, intermediate time-dependent covariates, and a possibly time-dependent outcome. Extensions include advice for the optimal discretisation of time¹³⁰ and to the hazard function.¹³¹

The one-step TMLE aims to preserve the performance of the original two-step TMLE, and achieves bias reduction in one step (i.e., without additional iterations of the TMLE update step and possible over-fitting in finite samples).¹³² This one-step TMLE was later extended to counterfactual average survival curves¹³³ and heterogeneous treatment effects.¹³⁴

The robust TMLE was proposed in 2017 for transporting intervention effects from one population to another.¹³⁵

The cross-validated TMLE (CV-TMLE) provides asymptotic inference under minimal conditions (i.e., non-parametric smoothness¹³⁶) keeping the bounds of the parameter estimates. It is also used in the estimation of data-adaptive target parameters, like optimal treatment regimes. Recently, TMLE was shown to be useful in defining thresholds and marking specified levels of risks.¹³⁷

The set of observational articles that use TMLE in their main or sensitivity analyses shows that TMLE has successfully been used to examine associations, ^{12,14,20–22,24,26,28,29,31,32,34,35,37,39,40,42–44,46–48,51–54,56–63,65,72–76,79,81,85,88–90} causation, ^{13,15–19,23,25,33,36,38,45,49,50,55,64,66–68,70,71,77,78,80,82–84,86,87,91,97} and variable importance. ^{12,20,65,86} It has been used to analyse

data with varying numbers of observations, from less than 100 to over hundreds of thousands, from clinical trials, cohort studies, ^{13,14,17–19,25,26,32,33,36,38–40,43,46,49,50,52,55,58–61,63,70,73–75,77,78,84–91} and observational studies.



FIGURE 3 Applied clinical and epidemiological research by year of publication and TMLE method implemented

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4 | DISCUSSION

We aimed to investigate the use of the TMLE framework in epidemiology and public health research and to describe the uptake of its methodological developments since its inception in 2006. We focused on TMLEs for point treatment, time-to-event/survival, and longitudinal exposure-outcome relationships. We did not discuss TMLE methodological developments and software for mediation analyses.^{138–140} We found that the TMLE framework and its different estimators were implemented in at least 81 epidemiological observational studies. The majority of these studies have come from the US, many of which are from the University of California, Berkeley. Recently, the use of TMLE has spread across the world. Until 2016, TMLE in observational studies was used by select groups of expertise and disciplines, such as biostatisticians or epidemiologists in academia exploring noncommunicable and infectious diseases, or behavioural epidemiology. From 2016 onward, there was a faster uptake amongst a wider range of expertise and disciplines. There is potential for even wider dissemination and acceptance, both geographically and in some specific disease areas or epidemiological disciplines. We hope this review of explicit and applied examples will contribute to enhancing the relevance of the TMLE framework and increasing its uptake and acceptance in settings where challenges with regard to data, unrealistic assumptions, or subject-matter knowledge lend themselves to the framework.

Initially, causal inference methods and estimators relied on parametric modelling assumptions but, to quote Box (1976), "all models are wrong but some are useful".¹⁴¹ It highlights that model misspecification was and remains a challenge, even with ever-growing datasets and computing power: exclusion of the unknown data-generating distribution leads to biased results. Semi-parametric and non-parametric causal inference estimators, such as AIPTW, double-debiased,¹⁴² and TMLE³ aim to provide the least biased estimate of the effect of an exposure on an outcome.^{1,143} Maximum Likelihood Estimation (MLE) based methods (stratification, propensity score and parametric regression adjustment) and other estimating equations (AIPTW) do not have all of the properties of TMLE, and evidence shows that they under-perform in comparison to TMLE in specific settings.^{1,3,5,120} For more detailed comparisons between the different methods, the interested reader is referred to Chapter 6 of van der Laan and Rose's TMLE textbook.² It is important to highlight that in contrast to the AIPTW estimator, TMLE respects the global constraints of the statistical model (i.e., P(0 < Y < 1) = 1) and solves the score estimation equations being equal to zero using substitution and fluctuation approaches.¹⁴⁴ TMLE augments the initial estimates to obtain an optimal bias-variance trade-off for the target estimand of interest and produces a well-defined, unbiased, efficient substitution estimator. Furthermore, the targeting step (i.e., update of the initial estimate) may remove finite sample bias. Lastly, the TMLE framework can be tailored to specific research questions that are difficult to answer using other causal inference methods, such as rare diseases, ^{145,146} ordinal ¹⁴⁷ or continuous exposures, ¹⁴⁸ dynamic treatment regimes, ¹²⁹ and missing outcome data.¹⁴⁹

We argue that dissemination of any new statistical methodology relies on five key factors: (i) software availability, (ii) accessibility of available material (e.g., quality of software help files, language used in publications, etc.), (iii) number of experts in the area, (iv) teaching, and (v) collaborations. In the following, we discuss the dissemination of TMLE with regard to each of them.

(i) Software availability:

Various TMLEs have been developed for complex study designs, such as those with time-to-event outcomes, case-control studies, hierarchical data structures (including cluster randomised trials), longitudinal data, and time-dependent confounding. These methodological developments were accompanied by the release of R software packages, increasing the usability of TMLE. Such software developments include the *SuperLearner*⁴ R package in 2007 and the *tmle* R package in 2012.¹⁵⁰ TMLE software for survival analysis (*survtmle*),^{151,152} longitudinal data (*ltmle*),¹⁰¹ doubly-robust confidence intervals (*dtrmle*),¹⁵³ and estimation of the survival curve under static, dynamic and stochastic interventions (*stremt*)¹⁵⁴ were implemented in 2017. To match the expanding framework, further software developments occurred in the following years, such as the *tlverse* suite of software packages for Targeted Learning (https://tlverse.org/tlverse-handbook/), which includes R packages for cross-validation (*origami*),¹⁵⁵ highly adaptive lasso (HAL, *hal9001*),^{156,157} super learning (*sl3*),¹⁵⁸ and TMLEs for a range of target estimands, such as effects under static interventions on an exposure (*tmle3*),¹⁵⁹ optimal dynamic treatment regimes for binary and categorical exposures (*tmle3mopttx*),¹⁶⁰ and stochastic treatment regimes that shift the treatment mechanism of a continuous exposure (*tmle3shift*).¹⁶¹ Additional recently developed packages in R include *ctmle* for collaborative TMLE,¹⁶² *haldensify* for conditional density estimation with HAL,^{163,164} *txshift* for estimating causal effects of stochastic interventions,^{165–167} and *lmtp*

for longitudinal modified treatment policies. 148

Although the TMLE framework is well developed in the R software, applied epidemiological research is performed in several other software languages, such as Stata, Python, and SAS. TMLE implementations for binary point exposure and outcome studies are available in all of these languages. A SAS macro for the general implementation of TMLE was programmed in 2016.⁹³ TMLE has been developed for the Python software language in the library *zEpid*.¹⁶⁸ The number of applied researchers in epidemiological studies using Python is relatively low but is increasing; thus, this tool is not currently widely used among applied health sciences researchers. Further development could improve on software packages in the widely used statistical software in health sciences and econometrics, such as Stata.¹⁶⁹ Nonetheless, the development version of the user-written Stata command *eltmle* is currently available to Stata users.¹⁶⁹ Not all features of TMLE are available in this Stata command, such as longitudinal analysis and cross-validated TMLE. Additionally, *eltmle* provides ensemble learning capabilities by accessing the *SuperLearner* R package. Lastly, any new software development needs to have a friendly user interface, together with standard programming features to be easily disseminated and quickly adopted.

(ii) Accessibility of available material:

The TMLE framework is a series of potentially statistically-complex modelling approaches and computational algorithms, grounded in statistical theory that requires a solid understanding of highly advanced statistics (i.e., theory for semi-parametric estimation, asymptotics, efficiency, empirical processes, functional analyses, and statistical inference). Tutorials in a more lay language targeting applied researchers and epidemiologists have become more common over the past five years and the uptake of TMLE is expected to increase in the future because of them. ^{1,5–7,93–96,103,120} Their beneficial impact is evident from this review, as these articles are highly referenced in applied work, from the year of their publication, alongside more methodologically heavy contributions to start with, and as sole references in later years. This shows evidence of the importance of speaking the language of the target audience and disseminating advanced mathematical statistics and algorithms from an applied perspective.

Additionally, the gradual dissemination of the TMLE framework was evident from our systematic review of the methods sections of the 81 selected manuscripts. We observed that papers published in the early years lay out their TMLE strategy and carefully describe each step in the methods section; whereas, more recently, publications of applied research have placed details of the methods in appendices (or supplementary material) and only cite tutorials and software packages. This shows that the community (e.g., authors, editors, reviewers, readers, etc.) is now aware of the TMLE framework, its utility, and its advantages. A wide range of journals have published the applied research articles studied here, from non-specific public health journals to statistical or disease-specific journals.

(iii) Experts:

Dissemination outside the US needs further work, as evidenced in our systematic review. We have shown that the TMLE framework appears to be well consolidated in the US, and adoption from Europe and other regions are lower in comparison. This may be related to the delayed introduction of causal inference education outside the US. Fostering targeted local seminars and dedicated short courses for the interested applied audience could be a useful strategy to disseminate the framework. Disease- or discipline-specific experts would be useful for the wider distribution of the methods in specific areas that would benefit from improved methodology.

TMLE remains dominant in non-communicable or infectious disease epidemiology compared to other disciplines, but it has high applicability in many disciplines and its use has increased in several of them. The slower uptake of the TMLE framework in other disciplines might be due to a lack of empirical examples of how one performed and interpreted statistical analyses using TMLE in a specific disease area. We aimed to provide such a showcase of the application of the methods in specific settings, based on the available literature, and we demonstrated how the framework was successfully used to advance research by providing robust results. We believe interested readers will find it useful to refer to the studies that faced similar challenges, or were based in settings comparable to theirs.

(iv) Teaching:

There have been tremendous efforts of dissemination of causal inference methods across disciplines, with a particular emphasis on epidemiology and econometrics sciences in the US during the last 20 years. Most graduate programs in epidemiology have included the teaching of causal inference as a leading topic in the field. In Europe, the trends have not been as fast-paced and for a long time, introductions to causal inference methods have mainly been provided through week-long intensive short courses and at international conferences. These different approaches have major impacts on how quickly the methods are adopted by the community of researchers, journal editors, public health groups, and regulatory agencies. In recent years, there has been a development and acceptance of real-world evidence in various public-health fields, such as the Food and Drug Administration's 21st Century Cures Act of 2016 in the US, which specifically promotes the use of causal inference methodology and designs, such as the emulated trial and TMLE frameworks.^{170–172}

(v) Collaborations:

The Center for Targeted Machine Learning and Causal Inference (CTML) is an interdisciplinary research centre at the University of California at Berkeley that is focused on applications of causal inference and targeted learning. The CTML mission is to advance, implement and disseminate methodology to address problems arising in public health and clinical medicine (https://ctml.berkeley.edu/home). CTML provides a great resource for courses, ongoing research, partners, collaborators, and Berkeley faculty members involved in TMLE. CTML sponsors include the Danish multinational pharmaceutical company, Novo Nordisk A/S, the Patient-Centered Outcomes Research Institute (pcori), Kaiser Permanente, the US National Institutes of Health, and the Bill and Melinda Gates Foundation. Academic partners include the University of Washington, University of Copenhagen, UCLA David Geffen School of Medicine, University of California at San Francisco, and Monash University.

Conclusions

Evidence shows that cross-validated, double-robust, efficient and unbiased estimators are at the forefront of causal inference and statistics, as they aim to avoid model misspecification, bias and invalid inference. The TMLE framework for causal and statistical inference was first developed in 2006 and its expansion in applied studies arose in 2018 via applied epidemiological work, tutorials and user-friendly software. The theoretical properties and practical benefits of the TMLE framework have been highlighted across different fields of applied research (such as various epidemiological, public health and clinical disciplines). More can be done to reach a wider audience across varied disease areas and scientific fields (e.g., genomics, econometrics, political and sociological sciences), including the development of software packages outside the R software, tutorial articles as well as seminars and courses targeted to audiences in specific disciplines, lay-language demonstration, such as by example, of the benefits of TMLE in improving epidemiological output, to name only a few ideas. Many recent TMLE developments answer a variety of methodological problems that expand across scientific disciplines and further efforts can be made to disseminate the framework. This would facilitate the conscientious application of TMLE for causal inference and statistical data analyses, so more researchers could use it in their applied work to minimise the risk of reporting misleading results that are biased due to misspecification.

FUNDING

This work was supported by the Medical Research Council [grant number MR/W021021/1]. A CC BY or equivalent licence is applied to the Author Accepted Manuscript (AAM) arising from this submission, in accordance with the grant's open access conditions. Camille Maringe is supported by a Cancer Research UK Population Research Committee Programme Award (C7923/A29018).

AUTHORS CONTRIBUTIONS

The article arose from the motivation to disseminate the principles of modern epidemiology among clinicians and applied researchers. All authors developed the concept and wrote the first draft of the article. MJS and CM reviewed the literature. MJS, RVP, MALF and CM drafted and revised the manuscript. RVP, SG and MJL provided comments on the draft manuscript. RVP contributed to drafting some sections. All authors read and approved the final version of the manuscript. CM is the guarantor of the article.

ACKNOWLEDGMENTS

The motivation and some parts of the manuscript come from MALF's work in a visiting academic position in the Division of Biostatistics at the Berkeley School of Public Health in 2019. We acknowledge Dr Susan Gruber for her careful read over one draft manuscript and Professor Mark J. van der Laan for his additional guidance.

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APPENDIX

Year	Development	First author	Related developments
2006	Seminal paper (TMLE)	van der Laan MJ	1
2009	Small sample size	Moore KL	Gruber S, 2010
	Case-control studies	Rose S	Rose S. 2011
			Balzer L. 2015
			Balzer L. 2016
2010	Collaborative TMLE	van der Laan MJ	Pirracchio R. 2018
	(c-TMLE)		Ju C. 2019
	Time to event data		Ju C. 2019
			Ju C. 2019
			Schnitzer ME. 2020
	Longitudinal data (LTMLE)	van der Laan MI	van der Laan, 2012
			Schomaker M. 2019
2012	Sequential randomised trials	Chaffee PH	5011011101111, 2017
	Natural direct effect	Zheng W	Lendle SD. 2013
		Lineng (Rudolph KE, 2018
	Non-independence	van der Laan MI	van der Laan MI 2014
			Schnitzer M 2016
			Sofrygin O 2017
			Balzer L. 2019
			Balzer L. 2021
2013	Meta-analysis / Safety outcomes	Gruber S	Lin Y 2022
2013	Pooled TMLE	Petersen M	Zheng W 2016
2011			Ferreira Guerra S 2020
	Interval-censored TMLE		
	Genetics	Wang H	Benkeser D 2019
		traing II	Yang G. 2022
2015	PS	Lendle SD	141.9 0, 2022
2010	Cross-validated TMLE	van der Laan MJ	
	cv-TMLE		
2016	One-step TMLE	van der Laan MJ	Cai W. 2020
2010			Zhu J. 2020
	TMLE for rare outcomes	Balzer L	Benkeser D. 2018
	TMLE for ordinal outcomes	 Díaz I	
2017	TMLE with missing outcome data	Díaz I	
	Robust TMLE	Rudolph KE	
	Targeted sequential inference of an optimal treatment rule	Chambaz A	
2018	Projected TMLE	Zheng W	
2019	TMLE for cluster-level exposure	Balzer L.B	
	Long-format TMLE	Sofrygin O	
	Highly-Adaptive least absolute shrinkage and selection	2011 / 5111 0	
2020	operator (LASSO) Targeted Minimum Loss Estimator	Cai W	
2020	(HAL-TMLE)	Cui II	
2022	Threshold response function	van der Laan MI	
2022	r mesnora response raneuon	van der Laan WIJ	

TABLE 1 TMLE methodological developments and their associated extensions

Authors Year Journal Disease area Research guestion Challenges Contribution to research Behavioural epidemiology Mackey DC et 2011 Am J Epidemiol Healthy living Physical activity and hip No RCTs Little difference in hip fracture risk for men with moderate or high physical activity al. Older age fracture levels relative to those with low physical activity level. Ahern J et al. 2016 Epidemiology Mental health Childhood adversities and Multidimensional exposure Childhood adversities play an important role in the burden of mental disorders in Childhood hardship mental disorders in adolescents, particularly for behavior disorders and to some extent for distress and Adolescent health adolescents substance disorders. Ethnicity However, despite the substantially higher burden of adversities experienced by black and Hispanic adolescents, they have a minor role in the patterns of disparities between racial/ethnic groups in mental disorders. Notably, fear disorders were the most common in all racial/ethnic groups, highest in black youth, and largely unrelated to childhood adversities Platt JM et al. 2018 Am J Epidemiol Childhood hardship Association between 11 Multidimensional exposure Interventions attempting to support and improve cognition in individuals who report IQ childhood adversities and childhood adversity can be a useful complement to interventions for emotional and intelligence behavioral disturbances Rodríguez-Occupational epi Improve knowldedge about Treatment effect heterogeneity We found that using an instructional video as educational intervention is an effective 2019 Int Arch Occup Molina D et al. approach to improve knowledge about preventive measures against occupational Environ Health Respiratory disease prevention against bias occupational asthma Low sample size asthma and allergies in Bavarian farm apprentices. High prop missing values Torres JM et al. 2019 Epidemiology Longitudinal relationships It may be that the long-term - but not short-term - absence of adult children had Migration Older age Is family-member migration Sample attrition adverse consequences for women's physical functioning as they aged into older Time-varying covariates Care associated with unmet adulthood. Deprivation caregiving needs among older We also found entirely null associations between having an adult child in the US and adults who remain in low and physical functioning for men. middle-income settings? Ehrlich SF et al. 2020 Am J Epidemiol Pregnancy / prenatal exposure Risk of small or large for Discussion of assumptions In underweight and normal-weight women only, meeting the lower exercise Healthy living gestational age according to Model mis-specification threshold recommended by the Physical Activity Guidelines for Americans also Birth outcomes exercise during 1st trimester appears to increase the risk of SGA and decrease the risk of LGA of pregnancy Bodnar LM et al. 2020 Am J Clin Nutr Nutritional epi Associations between fruit Dichotomisation of exposure TMLE produced effect estimates with less variation that suggested protective associations for diets high in fruits and vegetables relative to energy on risk of Pregnancy and vegetable intake relative Complex interactive effects between exposure and outcome preterm birth, SGA birth, and pre-eclampsia. to total energy intake and adverse pregnancy outcomes Multidimensional exposure Curse of dimensionality

TABLE 2 Articles by discipline

Kagawa RMC et 2020 Ann Epidemiol al.	Social epi Deprivation Mental health	Effect of fire arm involvement during violent victimization on the level of distress experienced and daily functioning within sociodemographic subgroups.	: Missing data	Victimization with a firearm is more distressing than victimization with another weapon or no weapon and that this response is almost universal across age, sex, race, and socioeconomic position.
Puryear SB et al. 2020 AIDS	HIV Alcohol	Assessing the effect of alcohol use across the entire cascade, from diagnosis to viral suppression.	l Longitudinal effects	Via the multiple steps of the cascade, HIV-positive drinkers had significantly worse viral suppression outcomes than non-drinkers.
Torres JM et al. 2020 Am J Epidemiol	Migration Older age Physical activity	Association between adult child US migration status and change in cognitive performance scores		
Clare PJ et al. 2020 Addiction	Alcohol Adolescent health	Effect of parental supply of alcohol on alcohol-related outcomes in early adulthood	Time-varying confounding Causal effects	Further evidence that parental supply of alcohol in adolescence has effects on a number of negative outcomes in early adulthood, including binge drinking and alcohol-related harm, leading not only to increased risk of binge drinking and harm but also increased frequency of binge drinking and number of harms experienced. Analysis of earlier initiation of supply showed that the magnitude of the effect of parental supply increased the earlier that supply was initiated
Kang L et al. 2021 J Safety Res		Risk-taking behaviors under various urban-street conditions, as a function of helmet use	Self selection Survey Heterogeneous effects Model mis-specification	Based on 131 survey participants, a significant positive risk compensation effect has been identified using the TMLE estimator and the size of effect is estimated to be about 15.6%.
Torres JM et al. 2021 Int J Geriatr Psychiatry	Older age Caring responsibilities Health outcomes	Evaluated the effect of spousal caregiving on multiple health outcomes in middle-aged and older adults in Mexico.	Reverse causality Survey waves Longitudinal data	Select evidence of adverse associations between spousal caregiving and past-week depressive symptoms: These adverse associations are generally described as the result of the emotional and physical burden of caregiving, which may have negative consequences for sleep, time for leisure and health promoting activities, and social isolation.
Lee JO et al. 2021 Public Health	Employment Mental health Covid-19	Examined the association of employment insecurity with two mental health measures, depression and anxiety	Reverse causality Missing data Sample weights	Employment insecurity has threatened mental health in the United States during the pandemic, and mental health repercussions are not felt equally across the population.

Shiba K et al.	2021 Epidemiology	Older age Mental health	We present an analysis that estimates and compares prevalence of depressive symptoms under alternattive hypothetical interventions in social participation.	Longitudinal data Survey waves Reverse causation Measurement bias/mis- classification	Past studies linking social participation and depressive symptoms in late life have not rigorously considered the time-varying nature of social participation. First study that explicitly estimated and compared the effects of alternative hypothetical interventions in social participation at two time points on subsequent depressive symptoms.
Ikeda T et al.	2022 J Affect Disord	Older age Mental health Strength	Examine the magnitude of the association between depressive symptoms over 2 years and weak handgrip strength among English people in 4 years of follow-up	e Survey waves Sample attrition - selection bias Self reported exposure	The main finding of our study was that people who maintained non-depressive symptoms or improved depressive symptoms were less likely to have weak handgrip strength than those with persistent depressive symptoms.
lkeda T et al.	2022 J Pain	Older age Physical activity	We hypothesized that older individuals who maintained physical activity over time tend to have a lower risk of low back pain, whereas those who discontinued activity were not.	Self reported exposure Small sample Sample attrition	Overall, the present study confirmed that maintaining physical activity reduced the risk of low back pain at the follow-up survey. Conversely, discontinuing activity (engaged only at the baseline survey) was not beneficial.
Biomarker epide Bembom O et al	emiology . 2009 Stat Med	Mutations Virology	Determine which of a set of candidate viral mutations affects clinical virologic response to the antiretrovira drug lopinavir + rank the importance of these mutations for drug-specific resistance	ldentify subset of relevant biomarkers I Biomarker importance	The subset of mutations identified by this approach as significant contributors to lopinavir resistance was in better agreement with the current knowledge than the subsets identified by an unadjusted analyses or the G-computation approach. In addition, the specific ranking provided by targeted VIM estimation also agreed better with the current understanding than did the rankings generated with alternative methods.
Rosenblum M et al.	2009 PLoS One	HIV Virology	Effect of adherence on viral load after different durations of viral suppression.	Selection bias Unmeasured confounding	These data suggest that for adherence proportions greater than 50%, the probability of virologic failure decreases with longer duration of viral suppression.
Gianfrancesco MA et al.	2016 Genes Immun	Genetics Ethnicity Skin disease	Examine clinically important marginal effects of a Genetic Risk Score composed of 41 established genetic risk loci on systemic lupus erythematosus activity over a period of 9 years	Little awareness of how genetic profiles have an impact on disease activity Longitudinal effects Time-dependent confounding Sample attrition	Results from individual SNP analyses provide important insight to the overall GRS findings; specifically, evidence for significant associations between certain SNPs and SLAQ score at two time points during the longitudinal study was demonstrated.

Hsu LI et al.	2016	Cancer Epidemiol Biomarkers Prev	Ethnicity Cancer Children health	Identify a list of candidate genes within each significantly enriched pathway in childhood Leukemia, while accounting in models, for the complex correlation between SNPs	Large, correlated data Data reduction Gene selection Variable importance	The results demonstrate that newly developed bioinformatics tools and causal inference methods may illuminate new and biologically relevant pathways and genes to improve current understanding of pathogenesis in childhood leukemia.
Salihu HM et al.	2016	Matern Child Health J	Ethnicity Pregnancy outcomes	Describe the methylation patterns of 20 candidate genes associated with preterm birth and evaluate their role in preterm births in African-American women.	Residual confounding	This study examined 42 CpG sites within 20 candidate genes previously linked to preterm birth and identified three CpG sites on 2 distinct genes (TNF-a and PON1) that were differentially methylated between black and nonblack newborns.
Izano MA et al.	2020	PLoS One	Birth Mental health	Evaluate the relationship between newborn telomere length and a comprehensive suite of chronic maternal stressors	Complex joint effects	We found that a greater proportion of Latina mothers reported financial strain, food insecurity, and high job strain, while a greater proportion ofBlack mothers reported poor neighborhood quality, experiencing stressful/traumatic life events, or having an unplanned pregnancy than other racial/ethnic groups.
Wang L et al.	2021	Front Genet	Cancer Environmental epidemiology	Identify tumor microenvironment-related genes to estimate their effects on the 3-year mortality of Ovarian cancer.	Variable selection Complex joint effects Model mis-specification	ARID3C, CROCC2, FREM2, and PTF1A were identified as prognostic biomarkers for OSC patients. Two of them (FREM2 and PTF1A), alongside CROCC, were successfully validated in three GEO datasets.
Sun X et al.	2021	Aging (Albany NY) Cancer	Identify the potential prognostic genes in the prostate adenocarcinoma microenvironment and estimate the causal effects simultaneously.	Causal effects Variable selection	Based on this strategy, we identified 14 genes involved in the prognosis of Prostate adenocarcinoma. The interaction between PRAD and TME might have serious effects on tumor evolution, further influencing tumor resistance, recurrence, and overall prognosis.
Environmental e	epidem	iology				
Padula AM et al.	. 2012	Am J Epidemiol	Prenatal exposure Birth outcomes	Estimate, at the population level, the predicted probability of term LBW had everyone been exposed to each quartile of traffic density.	Clear definitions of outcome and exposure + Previous inconsistent findings Measurement error Misclassification of exposure	The results did not show a clear exposure-response relation across the quartiles of traffic density; however, there was a significant difference in the predicted probability of LBW between the highest and lowest quartiles of exposure, showing that higher traffic density is associated with increased probability of LBW.

Herrera R et al.	2017	Int J Environ Res Public Health	Respiratory conditions Children health	Quantify the causal attributable risk of living close to the mines on asthma or allergic rhinoconjunctivitis risk burden in children	Assumptions discussed/checked Proxy measures of exposure Questionnaire Small sample size Missing outcome values	Results indicated that a hypothetical intervention intending to increase the distance from children's home to the mines could result in a reduction of rhinoconjunctivitis prevalence in the studied population by up to 4.7 percentage points (95% Cl: -8.4% ; -1.1%).
Pearl M et al.	2018	Paediatr Perinat Epidemiol	Life course epidemiology Pregnancy outcomes	Evaluate the separate and combined relations of neighbourhood opportunity in early-life and adulthood with pre-term birth risk in black, white and Latina women + assess the contribution of neighbourhood opportunity to racial-ethnic disparities in risk of PTB.	Longitudinal information	Our results do not point to a common susceptible period across racial/ethnic groups, possibly reflecting unmeasured heterogeneity of experiences represented by the poverty measure, or other unmeasured co-factors.
Rudolph KE et al.	2019	Environ Epidemiol	Adolescent health	Examine the relation between environmental noise and adolescent health in the US	Missing data - Multiple imputation Sampling weights Propensity score matching Different definitions for exposure Unmeasured confounding / measurement error	We found that living in a community where average day-night noise exceeded the US EPA safety guideline of 55 dB was associated with approximately 30–40 minute later bedtimes. Associations with DSM-IV mental disorders were mixed, generally with wide CIs, and not robust across sensitivity analyses.
Casey JA et al.	2019	Environ Res	Prenatal exposure	Do lower SES pregnant women have a heightened response to UNGD activity due to coexposure to other environmental and social stressors?	Missing data - Multiple imputation Exposure and outcome measure Assumptions discussed/checked	Our findings revealed an association between living in the highest quartile of a cumulative metric of UNGD activity during pregnancy and increased risk of antenatal anxiety or depression. This increased risk, however, did not appear to mediate the observed association between UNGD activity and preterm birth or reduced term birth weight, as we found no relationship between antenatal anxiety or depression and these outcomes in our sample.
Papadopoulou E et al.	2019	Environ Health Perspect	Prenatal exposure Biomarkers	Study the association between diet and measured blood and urinary levels of environmental contaminants in mother-child pairs from six European birth cohorts	Variable selection	We estimated that adherence to the dietary recommendations (pregnant women: ≤3 servings=week, children ≤2 servings=week) for fish intake would result in lower exposure to PFASs, As, and Hg compared with those exceeding these recommendation. Fruit consumption was associated with increased levels of urinary OP metabolites concentrations in both pregnant women and children. Using TMLE analysis, we found that consuming more than 2 fruits/d could increase the exposure of pregnant women to OPs, compared with lower fruit intake.

Nardone A et al.	. 2021	Environ Health Perspect	Historical epi	Assess the association between HOLC grade and 2010 normalized difference vegetation index (NDVI), a measure of overall greenness.		We found evidence of an association between worse historical HOLC grade and less 2010 greenspace using data from 102 U.S. urban metropolitan areas.
Health Economy	,					
Berkowitz S et al.	2019	Prev Chronic Dis	Financial resources and food insecurity, healthcare expenditure	Estimate the association between state- and county- level health care expenditures and food insecurity.	Unreliable assumptions in GLMs Ecological measures of exposure and outcome estimated	Adults who were food insecure had annual health care expenditures that were $$1,834$ (95% Cl, $$1,073-$2,595$) higher than adults who were food secure (P < .001). In children, the model-based estimate for health care costs associated with food insecurity was \$80 annually, but this finding was not significant (P = 0.53, 95% Cl, -\$171 to \$329).
Non-Communica	ble Dis	ease Epidemiology				
Legrand M et al.	. 2013	Crit Care	Post-operative, surgery, kidney	To determine the risk factors for post-operative acute kidney injury in patients operated on for inefective endocarditis.	Multifactorial reasons for the exposure-outcome association	Post-operative AKI following cardiopulmonary bypass for IE results from additive hits to the kidney. We identified several potentially modifiable risk factors such as treatment with vancomycin or aminoglycosides or pre-operative anemia.
Leslie HH et al.	2014	PLoS One	Hormonal contrception, cervical cancer	To determine whether potential risk factors such as hormonal contraception are true causes for cervical cancer amongst human immunodeficiency virus- positive women in developing countries.	Timing and duration of the exposure, type and measurement of the outcome.	Although selected results suggest an increased prevalence of cervical intraepithelial neoplasia 2 or greater (CIN2+) associated with combined oral contraceptive (COC), evidence is insufficient to conclude causality.
Mosconi L et al.	2018	PLoS One	Menopause, alzheimer's disease, cognitive performance	Examines the impact of the menopausal transition on Alzheimer's disease biomarker changes and cognitive performance in midlife	Alzheimer's disease is progressive and cross-sectional studies does not capture the ongoing AD process	the optimal window of opportunity for therapeutic intervention to prevent or delay progression of Alzheimer's disease endophenotype in women is early in the endocrine aging process.

Torres JM et al.	2018	Int J Epidemiol	Adult child migrant, mental health	We examined longitudinal associations between having an adult child migrant and mental health, for middle- aged and older Mexican adults accounting for complex time-varying confounding.	A doubly robust, semiparametric estimation strategy that reduces reliance on correct specification of multiple parametric models. Adjust for time-varying confounders affected by prior exposure	Women with at least one adult child in the US had a higher adjusted baseline prevalence of elevated depressive symptoms (RD: 0.063, 95% CI: 0.035, 0.091) compared to women with no adult children in the US. Men with at least one child in another Mexican city at all three study waves had a lower adjusted prevalence of elevated de- pressive symptoms at 11-year follow-up (RD: 0.042, 95% CI: 0.082, 0.003) compared to those with no internal migrant children over those waves.
Yu YH et al.	2019	Am J Epidemiol	Obesity, stillbirth	Estimated the association between incident obesity and stillbirth in a cohort constructed from linked birth and death records in Pennsylvania (2003–2013)	Time of onset of obesity is unknown, unclear whether estimated associations are driven largely by persons with long-standing obesity, recently developed obesity, or combination of both. Cause-effect interpretations rely heavily on assumptions if exposure cannot be randomised	we found positive associations of incident prepregnancy obesity with stillbirth
Lim S et al.	2019	Caries Res	Soda in-take, pediatric caries	Effect of soda intake on dental caries in young children (birth to 5 years).	Iongitudinal, time-varying data	consistent soda intake during the early childhood led to one additional caries tooth surface.
Gianfrancesco MA et al.	2019	J Rheumatol	Smoking, rheumatoid arthritis	Examined the association between smoking and rheumatoid arthritis.	Heterogeneous study designs, measurement error in key variables, biases in statistical anaylsis	Smoking is associated with higher levels of disease activity in RA.
Mozafar Saadati H et al.	2020	Obes Sci Pract	BMI, obesity, stroke, diabetics	Compared the effects of body mass index and central obesity on stroke in diabetics and non-diabetics.	Model misspecification, different distributions of the exposure between covariates	Among diabetics, body shape index and waist-to-hip ratio indices were associated with a higher incidence of stroke.
Veit C et al.	2020	BMC Med Res Methodol	Asthma, control medication	Calculate the long-term risk of reporting asthma symptoms in relation to control medication use in a real-life setting from childhood to adulthood.	RCT may not represent the general population	we did not observe a beneficial effect of asthma control medication on asthma symptoms.

Yu YH et al.	2020	Obstet Gynecol	Newly overweight and obesity, stillbirth	Identify the association of newly developed prepregnancy overweight and obesity with stillbirth and infant mortality.	Time-varying effects of covariates, timing of exposure	Transitioning from normal weight to overweight or obese between pregnancies was associated with an increased risk of stillbirth and neonatal mortality.
Decruyenaere A et al.	2020	Crit Care	Obesity, survival of critically ill patients	Association between obesity and improved survival among critically ill patients.	Failure to account for confounding and collider stratification bias	TMLE mitigates the obesity paradox observed in critically ill patients, whereas a traditional approach results in even more paradoxical findings
Abdollahpour I et al.	2021	Am J Epidemiol	Waterpipe smoke (vape), multiple scelrosis	Role of lifetime waterpipe smoking in the etiology of multiple sclerosis (MS).	Estimate marginal effects	these results suggest that waterpipe use, or strongly related but undetermined factors, increases the risk of multiple sclerosis.
Reilly ME et al.	2021	Foot Ankle Int	Symptomatic hallux valgus, clinical and radiographic outcomes, lapidus procedure vs scarf osteotomy	To compare clinical and radiographic outcomes between patients with symptomatic hallux valgus treated with the modified Lapidus procedure versus scarf osteotomy.	Positivity violations if not appropriately accounted for	Although the modified Lapidus procedure led to a higher probability of achieving a normal intermetatarsal angle, both procedures yielded similar improvements in 1- year patient-reported outcome measures
Torres LK et al.	2021	Thorax	acute respiratory distress syndrome, mortality,	To estimate the attributable mortality, if any, of acute respiratory distress syndrome (ARDS).	Adequately adjusted for confounders, and utilisation of statistical methodology to estimate causal effects	Acute respiratory distress syndrome has a direct causal link with mortality.
Mozafar Saadati H et al.	2021	Diabetes Metab Syndr	obesity, cardiovascular disease	To elucidate the effect modification of general and central obesity by sex and age on the risk of cardiovascular events.	Weakness and misspecification of statistcal models. Mediator effect of some biologic factors.	f Among males and age 54, waist-to-hip ratio index was associated with a higher risk of coronary heart disease and heart failure while body mass index was so for females and age>54.
Almasi-Hashiani A et al.	2021	BMC Public Health	reproductive factors, breast cancer	To estimate the causal effect of reproductive factors on breast cancer risk in a case- control study.	Misspecification of regression models may cause ex- treme bias in treatment effect estimates.	Postmenopausal women, and women with a higher age at first marriage, shorter duration of breastfeeding, and history of oral contraceptive use are at the higher risk of breat cancer

Dadi AF et al.	2021	BMC Pregnancy Childbirth	perinatal depression, infant diarrhea, acute respiratory infection, malnutrition	To estimate associations between perinatal depression and infant diarrhea, Acute Respiratory Infection (ARI), and malnutrition in Gondar Town, Ethiopia.	Differences in findings might potentially be due to bias as a result of unobserved confounding, which cannot be overcome using standard regression techniques	There was no evidence for an association between perinatal depression and the risk of infant diarrhea, acute respiratory infection, and malnutrition amongst women in Gondar Town.
					Failure to account for unobserved confounding can weaken the quality of evidence derived from such studies	
Zou R et al.	2021	Clin Nutr	maternal folate levels, pregnancy, neuropsychiatic disorders,	To estimate the association between prenatal exposure to folate and brain development (neuropsychiatric disorders) in late childhood has been rarely investigated.	Appropriately control for confounding	Low maternal folate levels during pregnancy are associated with altered offspring brain development in childhood, suggesting the importance of essential folate concentrations in early pregnancy.
Goel AR et al.	2021	J Am Acad Audiol	hearing aids, audiometric outcomes	To examine how hearing aids affect standard audiometric outcomes over long-term periods of follow-up.	Reduce bias due to study designs that have found differing evidence	Our analysis revealed discernible effects of 5 years of hearing aid use on hearing ability, specifically as measured by the PTA3-Freq, novel PTAExt, and WRS, suggesting a greater decline in hearing ability in patients using hearing aids
Beydoun HA et al.	2021	Sci Rep	brain metastases, stereotactic radiosurgery,	To compare hospitalization outcomes among US inpatients with brain metastases who received stereotactic radiosurgery (SRS) and/or non-SRS radiation therapies without neurosurgical intervention	Model misspecification	Stereotactic radiosurgery (SRS) alone or in combination with non-SRS therapies may reduce the risks of prolonged hospitalization and non- routine discharge among hospitalized US patients with brain metastases who underwent radiation therapy without neurosurgical intervention.
Chavda MP et al.	2022	J Crit Care	obesity, mortality, cardiac arrest	To estimate the conditional and causal effects of obesity on mortality in cardiac arrest patients using the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD).	Methodological issues leading to conflicting results.	After adjustment, there was no association between obesity and outcomes in cardiac arrest patients admitted to intensive care unit.

Crowner JR et al.	2022	Ann Vasc Surg	chronic limb threatening ischemia, nonoperative management	To assess whether chronic limb threatening ischemia (CLTI) objective performance goals (OPGs) could be attained with nonoperative management alone amongst patients with CLTI.		A comprehensive set treatment goals and expected amputation free survival outcomes can guide revascularization, but also assure that appropriate outcomes are achieved for patients treated without revascularization.
Akosile M et al.	2018	Int J Clin Biostat Biom	survival, right heart catheterisation	Investigated differences in survival among patients with and without right heart catheterisation using data from the Study to Understand Prognoses and Preferences for Outcomes and Risks and Treatments (SUPPORT)	Existence of unadjusted bias in the original analysis	Critically ill patients who received a right heart catheterisation had a significantly decreased 30-day and 60-day survival compared to patients who did not receive one after adjusting for a variety of potential con- founder selection strategies.
Infectious Diseas	e Epide	emiology				
Schnitzer ME et al.	2014	Biometrics	Hepatitis C virus, liver disease	Despite modern effective HIV treatment, hepatitis C virus (HCV) co-infection is associated with a high risk of progression to end-stage liver disease (ESLD) which has emerged as the primary cause of death in this population	identifying and adjusting for variables (baseline or time- varying) that affect both HCV clearance and ESLD Missing data	We found a clinically but not statistically significant protective effect of the clearance of hepatitis C virus on end-stage liver disease, adjusting for time in the model.
Davis FM et al.	2017	J Vasc Surg	Surgical site infection, graft failure	Surgical site infection after open lower extremity bypass, leading to increased rate of graft failure	structural or process-of-care character-istics of the hospitals where the procedures were performed	Surgical site infection after lower extremity bypass is associated with an increase in rate of amputation and reoperation
Vauchel T et al.	2019	Am J Infect Control	Imipenem-resistant acinetobacter baumannii (IR- AB), renal outcomes	To explore the impact of an outbreak of imipenem- resistant Acinetobacter baumannii (IR-AB) on renal outcomes.		The episode of imipenem-resistant Acinetobacter baumannii (IR-AB) outbreak was associated with an increased risk of kidney events, which appears to be driven by the use of colistin.

Kempker RR et al.	2020	Clin Infect Dis	Drugs for multidrug-resistant tuberculosis	Bedaquiline and delamanid are newly available drugs for treating multidrug-resistant tuberculosis (MDR-TB); however, there are limited data guiding their use and no comparison studies.	limited data on the clinical outcomes of patients treated with bedaquiline and delamanid under programmatic conditions,	Among patients with multidrug-resistant tuberculosis, bedaquiline-based regimens were associated with higher rates of sputum culture conversion, more favorable outcomes, and a lower rate of acquired drug resistance versus delamanid-based regimens
Westling T et al.	2020	Int J Infect Dis	Sepsis, aqueous chlorhexidine (CHG) used to reduce risk of bloodstream infections (BSI)	Assess the impact of bathing of neonates with 2% chlorhexidine solution on bloodstream infecitons, suspected sepsis, and mortality in a low-income country neonatal care unit.	Causal effects from observational data ncluding time-varying confounders	Aqueous chlorhexidine bathing at admission was associated with a reduced risk of bloodstream infections due to a pathogenic organism after adjusting for potential confounding.
Aiemjoy K et al.	2020	PLoS Negl Trop Dis	Distance from water source, chlamydia trachomatis, antibody reponses	Children living further from a water source would have higher exposure to Chlamydia Trachomatis and enteric pathogens as determined by antibody responses.	Flexible modelling approach to capture the relationship between seroprevalence and age	Children living further from a water source had higher seropreva- lence of S. enterica and G. intestinalis indicating that improving access to water in the Ethio- pia's Amhara region may reduce exposure to these enteropathogens in young children.
Figueroa S et al.	2020	Environ Res	Immune stimulation, acute lymphoblastic leukemia	we utilized targeted machine learning and traditional statistical methods to investigate the association of multiple measures of early immune stimulation with acute lymphoblastic leukemia (ALL) in Costa Rican children.	complex biological processes underlying immune dysregulation and leukemogenesis	Exposure to pets and farm animals was inversely associated with acute lymphobalstic leukemia risk, whereas having a fever longer than one week (a putative proxy of severe infection) was associated with an increased risk
Amusa L et al.	2021	BMC Public Health	male circumcision, sexually transmitted infections	Protective effect of male circumcision against some sexually transmitted infections (STIs)	Mimic an RCT	we present further evidence of a protective association of medical male circumcision against human immunodeficiency virus and herpes simplex virus type-2 in this hyperendemic South African setting.
Kerschberger B et al.	2021	Am J Epidemiol	anti-retroviral therapy, unfavourable health outcome	Same-day ART, effect on composite unfavourable treatment outcome	Assess real-world effectiveness	There was a reduced risk of composite unfavourable income amongst those with early anti-retroviral therapy initiation comapred to same-day anti-retroviral therapy.

Akhtar S et al.	2022	Mult Scler Relat Disord	hepatitis B vaccine, multiple sclerosis	HBV vaccine and multiple sclerosis risk	Marginal causal effect over a population	The results suggest a significant nonspecific protective effect of recombinant Hepatitis B vaccine against multiple sclerosis risk.
Chen C et al.	2022	J Nutr Health Aging	preoperative hs-crp/Albumin ratio and postoperative SIRS	preoperative hs-CRP/albumin ratio and SIRS	Interactions and stratified analysis	Preoperative hs-CRP/albumin ratio (CAR) was significantly associated with increased risk of postoperative SIRS in elderly patients.
Isfordink CJ et al.	2022	AIDS	Prevalence hepatitis C virus- viremia, direct-acting antivirals	Prevalence of HCV-viremia. Clinical determinants to lack of direct-acting antivirals	inference to settings with prolonged unrestricted access to treatment	Prevalence of hepatitis C virus-viremic amongst people with HIV is low in the Netherlands, coinciding with widespread DAA-uptake.
Figueroa S et al	. 2020	Environ Res	Immune stimulation, acute lymphoblastic leukemia	we utilized targeted machine learning and traditional statistical methods to investigate the association of multiple measures of early immune stimulation with acute lymphoblastic leukemia (ALL) in Costa Rican children.	complex biological processes underlying immune dysregulation and leukemogenesis	Exposure to pets and farm animals was inversely associated with acute lymphobalstic leukemia risk, whereas having a fever longer than one week (a putative proxy of severe infection) was associated with an increased risk
Occupational Ep	idemio	logy				
Brown DM et al	. 2015	Epidemiology	Particulate matter, heart disease	incidence of ischemic heart dis ease (IHD) in relation to accumulated exposure to particulate matter (PM) in a cohort of aluminum workers.	• Time-varying confounding, a component of the healthy worker survivor effect	The accumulation of exposure to PM2.5 appears to result in higher risks of ischemic heart disease in both aluminum smelter and fabrication work- ers.
Izano MA et al.	2019	Environ Epidemiol	Metalworking fluids, colon cancer	the relation between exposure to straight, soluble, and synthetic MWFs and the incidence of colon cancer in a cohort of automobile manufacturing industry workers	Time-varying confounding affected by prior exposure	evidence for a causal effect of straight metalworking fluids exposure on colon cancer risk
<u>Pharmacoepide</u>	miology	1				
Sukul D et al.	2017	J Invasive Cardiol	pre-procedural P2Y12 inhibitors, percutaneous coronary intervention (PCI).	assess the association between pre-procedural P2Y12 inhibitor administration and clinically important in-hospital outcomes.		Decline in the rate of pre-procedural P2Y12 inhibitor administration. No significant differences in outcomes between patients treated with pre-procedural P2Y12 inhibitors and those that were not

Bell-Gorrod H et 2020 Am J Epidemiol al.	human immunodeficiency virus–positive patients, mortality	assessed the impact of delayed switch from first-line ART treatment to second-line ART treatment on mortality in 9 South African treatment programs, a large cohort with long follow-up	Small patient numbers and limited follow-up times in previous studies	Early treatment switch is particularly important for patients with low CD4 counts at failure.
Rossides M et al. 2021 Respirology	methotrexate or azathioprine.	to estimate the relative risk of infec- tious disease at 6 months associated with the initiation of methotrexate compared to initiation of azathioprine in patients with sarcoidosis.		Methotrexate appears to be associated with a lower risk of infection in sarcoidosis than azathio- prine, but randomized trials should confirm this finding.
Kahkoska AR et 2021 Diabetes Care al.	treatment methods after positive test of SARS-COV-2 amongst adults.	determine the respective associations of premorbid glucagon-like peptide-1 receptor agonist (GLP1-RA) and sodium–glucose cotransporter 2 inhibitor (SGLT2i) use, compared with premorbid dipeptidy1 peptidase 4 inhibitor (DPP4i) use, with severity of outcomes in the setting of severe acute respiratory syn- drome coronavirus 2 (SARS- CoV-2) infection.	Residual confounding	Among SARS-CoV-2–positive adults, premorbid GLP1-RA and SGLT2i use, compared with DPP4i use, was associated with lower odds of mortality and other adverse outcomes, although DPP4i users were older and generally sicker.
Policy Tran L et al. 2016 Epidemiol Methods	Human immunodefficiency virus, low-risk express care task-shifting program	estimating the joint effect of both time to availability of a nurse-based triage system (low risk express care (LREC)) and individual enrollment in the program among HIV patients in East Africa	Point effect of one or more longitudinal exposures, or a series of sequential treatment decisions	small impact of both availability and enrollment in the low risk express care program on incare survival.
Skeem JL et al. 2017 JAMA Psychiatr	y Traditional probation, specialty mental health probation	To test whether specialty probation yields better public safety outcomes than traditional probation.	Short follow-up, limited covariate set	well-implemented specialty probation appears to be effective in reducing general recidivism.

Skeem JL et al.	2018 Psychiatr Serv	Costs or traditional and specialty probation	Specialty mental health probation reduces the likelihood of rearrest for people with mental illness	Small sample size	Well-implemented specialty probation yielded substantial savings—and should be considered in justice reform efforts for people with mental illness.
Mehta B et al.	2021 Arthroplast Today	Primary care physicians (PCPs) density and total knee and total hip arthroplasty outcomes.	To examine the relationship of primary care provider density with total knee arthroplasty and total hip arthroplasty outcomes.	Missing data, zero inflation	no statistically significant association between PCP density and pain, function, or stiffness outcomes at baseline or 2 years.
Wong AK et al.	2022 Epidemiology	Public masking mandates, COVID-19 cases and deaths	evaluating the effect of delays in state-level public masking mandates on the relative growth of COVID-19 cases and deaths in the 50 US states from 1 September to 31 October 2020.	Relience on epidemic modelling	public masking mandates are asso-ciated with population-level reductions in COVID- 19 spread
Moreno- Betancur M et al.	2022 Int J Epidemiol	Child development	Evaluate effects on child developmental vulnerability after long-term follow up of a family home visiting program.	Mixed evidence from RCTs, target trial to provide suitable evidence	Results did not provide robust evidence of meaningful beneficial or adverse effects of family home visiting program on child development vulnerability.
You Y et al.	2019 BMC Med Inform Decis Mak	type 2 diabetes, health programme	assess the performance of a multidisciplinary-team diabetes care program called DIABETIMSS on glycemic control of type 2 diabetes (T2D) patients	Not possible to evaluate a new programme by design, impractical to randomise the initiation	DIABETIMSS program had a small, but significant increase in glycemic control