

**EVALUATION OF METHODS TO DETECT
LEGACY EFFECTS IN CARDIOVASCULAR
POST-TRIAL STUDIES**

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A THESIS SUBMITTED IN FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF

Doctor of Philosophy

School of Public Health, Faculty of Health
Univeristy of Technology Sydney

2021

Certificate of Original Authorship

I, Lin Zhu declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Public Health, Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

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Abstract

Post-trial follow-up studies after randomized controlled trials (RCT) are increasingly used to investigate the clinical effectiveness of an intervention in the long term. “Legacy effect”, which was proposed in the context of such studies, describes the effects of an intervention that are only observed after the end of trial and are not due to the direct effects observed during the trial period itself. Much of the clinical interest in legacy effects has been in the drug treatments for cardiovascular disease prevention, as the finding of such effect could provide support for earlier initiation of the intervention. However, limited attention has been paid to the methodological challenges of analysing post-trial data.

In this thesis, I provide a summary of the methods used, and evaluate the potential for bias, in the cardiovascular post-trial studies. I also investigate how we might best analyze data from a matching RCT and post-trial follow-up study, specifically, the choice of time period and trial participants to include in analysis and the strategy to correct for potential selection bias and confounding. Simulations are conducted to compare the performance of different methods. I use data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and its follow-up data to illustrate the application of different approaches.

Analyses combining both the initial trial period and the post-trial follow-up period have often been incorrectly interpreted as evidence of a legacy effect, which is better assessed on the basis of separate post-trial analysis. To address the issues of selection bias and potential confounding requires appropriate study designs and rigorous methods of analysis. The choice of statistical methods should consider the availability of post-trial data, size of direct treatment effect and causal pathway of legacy effect. It is recommended to conduct a sensitivity analysis to check the robustness

of the findings. Better reporting of legacy effects is needed to realize their full value in informing clinical practice and health policy.

Acknowledgements

First and foremost, I would like to thank my two supervisors, Professor Andrew Hayen and Associate Professor Katy Bell, for their patient guidance, invaluable advice and huge investment of time in me. It has been a privilege to work under their supervision over the past four years. Andrew gave me the freedom to pursue my study interest and provided his best support. His positive outlook in my research inspired me and made me more confident. Katy provided a great deal of insightful feedback on my research ideas and written works, from where I learnt a lot. Her enthusiasm for research has always motivated me to work harder and aim higher.

I gratefully acknowledge the funding received towards my Ph.D. from Australian Government Research Training Program Scholarship. I am also grateful to University of Technology Sydney for providing me the financial support to attend conferences and training courses. I thank the National Heart, Lung, and Blood Institute for providing the data used in this thesis.

I would also like to thank my colleagues and staff members in the Faculty of Health, Sarita, Kirsten, Krishna, Pauline, Penny, Zhuoyang, Priya and Julia for their support and encouragement along the way. I am grateful to my friends, Lei, Peng, Tao, Yu, Zhaoqing, Juanwen and Xiaohang, for their help in my study and life, and the wonderful times we shared in Sydney.

Finally, I wish to express my deepest gratitude to my partner and parents. This would not have been possible without their unselfish support and love at all times.

List of Publications

Journal Publications

1. **Zhu L**, Bell K, Nayak A, Hayen A. A Methods Review of Post-trial Follow-up Studies of Cardiovascular Prevention Finds Potential Biases in Estimating Legacy Effects *Journal of Clinical Epidemiology* 131, 51-58 (2021)
2. **Zhu L**, Hayen A, Bell K. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. *Cardiovascular Diabetology* 19, 28 (2020)
3. **Zhu L**, Bell K, Hayen A. Estimated legacy effects from simulated post-trial data were less biased than from combined trial/post-trial data. *Journal of Clinical Epidemiology* 114, 30–37 (2019).
4. Nayak A, Hayen A, **Zhu L**, McGeechan K, Glasziou P, Irwig L, Doust J, Gregory G, Bell K. Legacy effects of statins on cardiovascular and all-cause mortality: A meta-analysis. *BMJ Open* 8, 1–11 (2018)*

Conference Publications

1. **Zhu L**, Bell K, Hayen A. Using marginal structural models to account for selection bias in the analysis of legacy effect. *2020 World Congress of Epidemiology*
2. **Zhu L**, Bell K, Hayen A. Statistical methods for estimating legacy effect: a simulation study. *2018 Australasian Epidemiological Association Annual Scientific Meeting*

*This article was published during my candidature. It is not a part of this thesis.

3. **Zhu L**, Hayen A, Bell K. Research methods for detecting legacy effect: a scoping review. *2017 Australasian Epidemiological Association 30th Anniversary Scientific Meeting*

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Abbreviation

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORDION	Action to Control Cardiovascular Risk in Diabetes Follow-on
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
DAG	Directed Acyclic Graph
HbA1c	Hemoglobin A1c
HDL	High-density Lipoprotein
HF	Heart Failure
HR	Hazard Ratio
IPW	Inverse Probability Weighting
LDL	Low-density Lipoprotein
MI	Myocardial Infarction
MSE	Means Square Error
MSM	Marginal Structural Model
PS	Propensity Score
RCT	Randomized Controlled Trial
SD	Standard Deviation
SE	Standard Error
T2DM	Type 2 Diabetes Mellitus
TRIG	Triglycerides