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Applying quasi-experimental methods to establish causal impacts of large-scale disease prevention interventions

Michaela Johanna Theilmann

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Vorsitz: Prof. Dr. Michael Laxy

Prüfer*innen der Dissertation:

1. Prof. Nikkil Sudharsanan, Ph.D.
2. Assistant Prof. Jennifer Manne-Goehler

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List of abbreviations

BCG	Bacillus Calmette–Guérin
CARRS	Centre for Cardiometabolic Risk Reduction in South Asia
DiD	Difference-in-Differences
HMD	Human Mortality Database
LATE	Local average treatment effect
MSE	Mean squared error
MTM	Makkalai Thedi Maruthuvam
NMAP	National Multisectoral Action Plan for Prevention and Control of Common Non-Communicable Diseases
NPCDCS	National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke
pp	Percentage points
RCT	Randomized controlled trial
RDD	Regression Discontinuity Design
RKD	Regression Kink Design
WHO	World Health Organization

Abstract

Randomized controlled trials are regarded as the gold standard for evaluating the effectiveness of health interventions. However, their implementation can be complex and may not always be feasible for assessing the impact of large-scale disease prevention policies. In such cases, quasi-experimental methods can serve as a valuable alternative for estimating causal effects. Despite their large potential, these methods are underutilized in public health research. In my thesis, I demonstrate how quasi-experimental methods can be used in a variety of contexts using different data sources to establish causal impacts of population prevention programs. Specifically, I show how the Regression Discontinuity Design, its modification the Regression Kink Design, and the multi-period Difference-in-Differences can be applied to evaluate two different large-scale disease prevention policies.

In the first study, I investigated the potential *non-specific* effects of the Bacillus Calmette–Guérin (BCG) vaccine, developed to protect against tuberculosis, on survival into adulthood. In recent years, there has been increasing scientific interest in the vaccine's non-specific effects, i.e. beneficial health effects other than those directly related to tuberculosis. While evidence on these non-specific effects among adults is scarce, a recent study from Denmark estimated a 42% lower probability of survival into adulthood among those who did not receive the vaccine compared to those who did. However, this and the other existing studies do not sufficiently account for confounding factors, and thus the estimated associations cannot be considered causal relationships. Using data on cohort mortality rates for birth cohorts born from 1950 to 1988 in Sweden, I employed the Regression Discontinuity Design to estimate whether the sudden discontinuation of the population vaccination scheme in 1975 had a causal effect on the probability of survival to age 30. This analysis revealed that the probability of survival did not change in the total population (0.00 percentage points (pp) (95% CI -0.46 - 0.27), among

females (-0.18pp (-1.05 - 0.70)) or males (0.05pp (-0.26 - 0.32)). These results were confirmed by estimating the Regression Kink Design and the multi-period Difference-in-Differences models. Because of the large sample size (> 4 Million observations), the null results are precisely estimated and thus suggest no medically meaningful effects. Thus, it can be concluded that the BCG vaccine did not seem to have non-specific effects on survival into adulthood in Sweden, which contradicts previous evidence from Denmark. Future research should investigate whether specific sub-groups, such as individuals suffering from certain diseases, could benefit from potential non-specific effects of the BCG vaccine.

In the second study, I examined whether a home-based hypertension screening initiative in India led to an increase in formal hypertension diagnosis and treatment. Uncontrolled hypertension is the main risk factor for cardiometabolic diseases such as stroke and heart attack. Given the low rate of controlled hypertension in India, the government is increasingly investing in home-based screening initiatives to improve linkage to care. These initiatives involve health care staff visiting individuals in their homes to measure blood pressure and provide health education and referrals to a health care facility for formal diagnosis and treatment initiation, as needed. For home-based screening to be effective, it is pivotal that individuals act upon the health information received, visit a health care center for formal hypertension diagnosis, and then initiate and adhere to the treatment. Otherwise, home-based screening cannot contribute to the improvement of hypertension control. Despite the Indian government's investment in these programs, there is no evidence to date on whether home-based screening increases the uptake of hypertension care in India. To address this knowledge gap, I analyzed panel data from six waves of a household survey conducted between 2010 and 2018. The data are representative of adults aged 20 years and older living in Delhi and Chennai, two of the largest cities in India. I applied the Regression Discontinuity Design and find that home-based

screening did not increase formal hypertension diagnosis or treatment in the total population, among males, or females. Disaggregating the analysis by education category, age group, previous diagnosis of cardiometabolic diseases, or city of residence also showed no statistically significant effect in any of these population groups. Before further scaling up home-based screening initiatives in India, it should be investigated why individuals do not act upon the health information received and how home-based screening can be designed to better address the needs of the population.

In conclusion, my dissertation provides valuable insights into the causal impacts of two population-level disease prevention interventions and emphasizes the significance of rigorous evaluation methods. By demonstrating how quasi-experimental methods can be applied, my research highlights an alternative approach to randomized controlled trials, particularly in situations where randomized treatment assignment is not possible. The use of quasi-experimental methods can offer important benefits for policy makers and researchers in the public health realm and their utilization should be considered more widely.

Zusammenfassung

Randomisierte kontrollierte Studien (RCT) sind der derzeitige Goldstandard der Wirkungsevaluation von Gesundheitsinterventionen. Die Evaluierung großflächiger Präventionsmaßnahmen durch eine RCT ist jedoch oftmals komplex oder nicht umsetzbar. Wenn eine Randomisierung nicht möglich ist, können quasi-experimentelle Methoden eine wertvolle Alternative für die Schätzung kausaler Zusammenhänge sein. Trotz ihres großen Potentials werden diese Methoden in der Gesundheitsforschung kaum angewandt. In meiner Doktorarbeit zeige ich, dass quasi-experimentelle Methoden in unterschiedlichen Kontexten und mit verschiedenen zugrundeliegenden Datenquellen kausale Effekte von Präventionsmaßnahmen schätzen können. Anhand des Regression Discontinuity Designs, des Regression Kink Designs und der multi-period Difference-in-Differences Methode evaluiere ich zwei großflächige Krankheitspräventionsmaßnahmen.

In der ersten Studie untersuche ich, ob die Bacillus Calmette-Guérin (BCG) Impfung gegen Tuberkulose nicht-spezifische Effekte auf die Erreichung des Erwachsenenalters hat. Diese nicht-spezifischen Effekte, also positive Gesundheitseffekte neben des Schutzes gegen Tuberkulose, haben über die letzten Jahre zunehmend das Interesse der Forschungsgemeinschaft geweckt. Allerdings gibt es bisher wenige robuste Erkenntnisse: Beispielsweise zeigt eine Studie aus Dänemark, dass Individuen, die die BCG Impfung nicht verabreicht bekamen im Vergleich zu denen, die sie verabreicht bekamen, eine 42% niedrigere Wahrscheinlichkeit haben das Erwachsenenalter zu erreichen. Jedoch sind die angewandten statistischen Methoden dieser und anderer vorheriger Studien nicht geeignet um Störfaktoren ausreichend zu minimieren. Deswegen sollten die Ergebnisse dieser Studien nicht als kausale Zusammenhänge sondern als Korrelationen interpretiert werden. Ich nutze Daten der Jahrgangssterblichkeit der Geburtenjahrgänge 1950 bis 1988 in Schweden und schätze, ob sich

die abrupte Beendigung der verpflichtenden BCG Impfung im Jahr 1975 auf das Erreichen des Alters von 30 Jahren auswirkt. Anhand des Regression Discontinuity Designs zeige ich, dass die Überlebenschance in der Gesamtbevölkerung (0.00 Prozentpunkte (pp) (95% CI -0.46 - 0.27), unter Frauen (-0.18pp (-1.05 - 0.70)) und Männern (0.05pp (-0.26 - 0.32)) nicht beeinträchtigt wurde. Die Regression Kink Design und multi-period Difference-in-Differences Analysen bestätigen dieses Ergebnis. Wegen der großen Stichproben (> 4 Millionen Beobachtungen) sind diese Ergebnisse präzise Schätzungen und der Nulleffekt ist kein Resultat einer schwachen Teststärke. Diese Ergebnisse legen nahe, dass die BCG Impfung keine nicht-spezifischen Effekte auf die allgemeine Überlebensrate in das Erwachsenenalter hat, was den Ergebnissen der Studie aus Dänemark widerspricht. Es sollte weiter erforscht werden, ob bestimmte Bevölkerungsgruppen, zum Beispiel Menschen, die unter bestimmten Krankheiten leiden, von potentiellen nicht-spezifischen Effekten der BCG Impfung profitieren könnten.

In der zweiten Studie evaluiere ich, ob häusliches Hypertonie-Screening zu einem Anstieg formeller Hypertoniediagnosen und -behandlung in Indien führt. Hypertonie ist der Hauptrisikofaktor für kardiometabolische Erkrankungen (zum Beispiel Herzinfarkt oder Schlaganfall). Da der Anteil der Hypertonieerkrankten mit kontrolliertem Blutdruck niedrig ist, investiert die indische Regierung zunehmend in häusliche Screening-Programme, um die Anbindung dieser Menschen an das Gesundheitssystem zu verbessern. Im Rahmen des häuslichen Screenings werden Hausbesuche durchgeführt und Blutdruck gemessen. Personen mit erhöhtem Blutdruck werden Informationen zu Hypertonie übermittelt und an ein Gesundheitszentrum für eine formale Diagnose und Behandlungsbeginn überwiesen. Damit häusliches Screening einen Effekt entfalten kann, müssen die Informationen und Überweisung befolgt, ein Gesundheitszentrum aufgesucht und Diagnose und Medikamente erhalten werden. Wird die Überweisung ignoriert, kann häusliches Screening nicht zur Blutdruckkontrolle

beitragen. Derzeit gibt es keine Forschungsergebnisse, die zeigen, ob häusliches Screening in Indien die Inanspruchnahme von Gesundheitsleistungen für Hypertonie beeinflusst. Um diese Wissenslücke zu schließen, nutze ich Paneldaten aus sechs Runden einer Haushaltsbefragung in Indien, die zwischen 2010 und 2018 durchgeführt wurden. Die Daten sind repräsentativ für Erwachsene im Alter von 20 Jahren oder älter in Delhi und Chennai, zwei der größten Städte Indiens. Die Ergebnisse der Regression Discontinuity Design Analyse zeigen, dass häusliches Screening weder formale Diagnose einer Hypertonie noch den Behandlungstatus beeinflusst. Dieses Ergebnis findet sich auch in unterschiedlichen Bildungskategorien und Altersklassen wieder, und ist ebenfalls unabhängig von einer vorherigen Diagnose einer kardiometabolischen Erkrankung oder des Wohnorts (Chennai oder Delhi). Bevor indische Regierungen vermehrt in häusliches Screening investieren, sollte untersucht werden, wieso Individuen der Überweisung nicht folgen und wie das häusliche Screening gestaltet sein müsste, um die Menschen adäquater anzusprechen.

Meine Doktorarbeit schätzt die kausalen Effekte zweier großflächiger Präventionsmaßnahmen. Ich zeige, wie quasi-experimentelle Methoden angewandt werden können und generiere neue Einblicke in die Evaluierung von Präventionsprogrammen. Quasi-experimentelle Methoden sind eine wertvolle Alternative zu RCTs, wenn Randomisierung nicht möglich ist. Forschende und politische Entscheidungsträger im Gesundheitswesen sollten deren Nutzung öfter in Betracht ziehen.

1. Estimating causal effects of disease prevention policies

Disease prevention is an important component of maintaining or improving a population's health status. While primary prevention aims to reduce the risk of an individual developing a disease, the objective of secondary prevention is to detect, treat, and control a disease as soon after its onset as possible and before it becomes symptomatic.[1] If adequately designed, preventive measures have the potential to reduce the health burden and also health care spending as diseases do not develop in an individual or, in the case of secondary prevention, are controlled before becoming severe and requiring more intense and expensive treatment.[2] The World Health Organization (WHO) estimates that every US dollar invested in the prevention and control of non-communicable diseases would return seven US dollars by 2030.[2] Their set of 16 "best buys", which are highly cost-effective measures to prevent and control non-communicable diseases, include population policies such as the vaccination of girls aged 9 to 13 years against the human papillomavirus to prevent cervical cancer and the control of hypertension as a risk factor for cardiovascular disease.[2] Despite their cost-effectiveness, large-scale population prevention programs can be resource intensive and it is, thus, crucial to know what works in the context of a specific health condition and target population.

The current gold standard for evaluating health interventions is the randomized controlled trial (RCT).[3,4] In RCTs, participants are randomly assigned to either the treatment group, which receives the intervention, or the control group, which does not receive the intervention. The general underlying assumption is that the random allocation of participants accounts for observable and unobservable confounding, which results in an equal distribution, on average, of participants' characteristics across the two groups.[5,6] Thus, to estimate the effect of the intervention of interest, the outcome among individuals in the treatment group can be compared

to the outcome among those in the control group. The difference is the estimated treatment effect. Conducting RCTs, in particular to evaluate large-scale population prevention programs, can be challenging and even unfeasible for a variety of reasons. First, the random allocation of a policy might not align with policy priorities. Implementing agencies, such as governments or non-governmental organizations, might prioritize individuals or areas with the largest disease burden and thus the largest need for preventive measures.[7] They might also prefer to focus on specific geographic regions, such as urban centers or selected administrative districts.[7] Additionally, the implementation of an RCT needs to follow a strict order of actions and timeline. Governments, however, might be constrained in their decision when to implement as they depend on the availability of monetary funds and other resources.[7] Complex RCTs that require substantial preparative work or long periods for potential effects to unfold may also be seen as a less attractive option as they might not align with policy cycles, such as the timing of elections or budgeting.[7] In addition to that, RCTs only provide an assessment of one point in time. The setting up of a monitoring system might seem a more worthwhile investment to governments as it produces tangible results sooner and can be used for continuous knowledge creation.[8] Another concern by policy makers might be the risk of perceived unfairness by the population that is allocated to the control group.[7] Even if the plan is to scale up the prevention policy if found to be effective, the potential backlash from the population during the trial might discourage governments from randomizing treatment assignment.[7] Second, randomizing an intervention is unethical if it is known to be beneficial or if participants could be harmed.[7] For example, a government wants to test different ways of improving childhood immunization coverage and randomly allocates individuals to the treatment group (vaccination during home visits) and to the control group (vaccination in health centers, the standard of care). This RCT would be considered ethical because all individuals continue to have access to the vaccine in health centers and it is unclear whether home visits increase vaccination uptake. If, however,

the vaccine was new, readily available, and known to be effective, it would be considered unethical to only offer it to individuals in the treatment group. Although the first case would be ethical from a research perspective, it might still be perceived as unethical from the policy makers' and populations' perspectives as it does not offer the same benefits to everyone. In these cases, policy makers might also prefer to not conduct an RCT. Third, certain large-scale interventions, such as the construction of a new hospital, cannot be randomized because it is not feasible to randomly select the hospital's location or determine which individuals will use its services. The same challenge applies to policies implemented at the national scale simultaneously, such as population vaccination schemes. Fourth, a policy might already have been implemented without any consideration of an impact evaluation. In these cases, a randomized assignment is not feasible anymore. Without randomization, it becomes difficult to establish a causal effect of a policy by simply estimating the difference in the outcome between those who received an intervention and those who did not, as they will most likely differ systematically in their characteristics.[7]

In situations, when an RCT is not feasible or was not done, quasi-experimental methods represent a valuable approach for assessing the effectiveness of a health intervention. In addition to their potential to estimate causal effects in the absence of randomization, there are several other strengths in comparison to RCTs: (1) RCTs, in particular clinical trials, often have strict inclusion criteria, which might exclude relevant population groups such as individuals with comorbidities or certain age ranges.[9,10] Quasi-experiments can produce more generalizable results, i.e. results with a higher external validity, because they commonly use data that are more representative of the population which will ultimately be covered by the intervention. (2) Quasi-experiments evaluate a "real life" situation.[9] RCTs create an artificial environment in which the implementation is often designed in a way that is expected to be most

effective and in which particular focus is put on implementation fidelity and participants' compliance with the treatment.[7] While this might maximize the benefit of an intervention, it might not be possible to sustain these efforts at a larger scale and over long time periods. A quasi-experiment evaluates a policy as it is implemented in reality, which reflects the changes induced by a policy under natural rather than artificial circumstances. (3) Conducting a quasi-experiment usually incurs lower costs.[7,11] If secondary data are used, costs for data collection, which can be substantial, are saved. But also costs related to the implementation of the RCT, such as hiring staff and setting up the infrastructure required solely for the experiment, are not incurred.

The definition of "quasi-experimental method" varies across disciplines. In the scope of this thesis, I refer to the four most commonly applied quasi-experimental methods in development economics: (1) Difference-in-Differences (DiD), (2) Instrumental Variable, (3) Matching, and (4) Regression Discontinuity Design (RDD).[7] Rather than relying on the random assignment of individuals to the treatment or control group, quasi-experimental methods aim to construct a comparison group, the "counterfactual".[12] If a quasi-experimental method's assumptions are fulfilled, it is assumed that the counterfactual represents the outcome that would have materialized in the treatment group had they not received the intervention. Thus, the difference in the outcome between the treatment group and the counterfactual can be interpreted as the causal effect of an intervention. Despite their large potential in public health research, quasi-experimental methods are underutilized.[13,14]

The objective of my dissertation is to show how quasi-experimental methods can be employed to evaluate large-scale disease prevention programs in the absence of random assignment to a

treatment or control group. I will show the versatility of quasi-experimental methods by estimating causal effects of two large-scale population prevention programs, in two different country contexts, and using two different data sources (Table 1). First, in the "BCG study", I investigated whether childhood Bacillus Calmette–Guérin (BCG) vaccination had non-specific effects, i.e. beneficial health effects other than those directly linked to tuberculosis, the disease it was developed for. Specifically, I looked at the vaccine's effect on survival into adulthood. For this, I made use of the fact that Sweden abruptly discontinued the compulsory population BCG vaccination policy in 1975. I used mortality rates of birth cohorts born before and after the sudden discontinuation and employed the RDD, its modification the Regression Kink Design (RKD), and the DiD. Second, in the "home-based screening" study, I assessed whether home-based hypertension screening increased formal hypertension diagnosis and treatment in India. I used data from multiple waves of a panel household survey representative of the population aged 20 years and older living in two large Indian cities and employed the RDD.

Table 1: Application of quasi-experimental methods in this dissertation

	BCG study	**Home-based screening study**
Intervention	BCG vaccine	Home-based hypertension screening
Outcome	Survival to age 30	Hypertension diagnosis Hypertension treatment
Country	High income (Sweden)	Lower-middle income (India)
Data	Census	Survey
Methods	multi-period DiD, RDD, RKD	RDD

Abbreviations: BCG = Bacillus Calmette–Guérin; DiD = Difference-in-Differences; RDD = Regression Discontinuity Design; RKD = Regression Kink Design

This dissertation is organized as follows: Chapter 2 comprises the BCG study starting with the overview and background of the study in Sections 2.1 and 2.2. In Section 2.3, I present the data and describe the outcome. In Section2.4, I explain the three quasi-experimental methods, RDD, RKD, and multi-period DiD, and their application in the BCG study. In Section 2.5, I present the results, which I discuss in Section 2.6. Chapter 3 consists of the home-based screening study. After presenting the overview and background of the study in Sections 3.1 and 3.2, I describe the data and outcomes in Section 3.3 and explain how the RDD was applied in this study in Section 3.4. In Section 3.5, I present the results and discuss them in Section 3.6. The final chapter, Chapter 4, concludes and assesses the potential of quasi-experimental methods in public health research.

2. The BCG study

2.1 Rationale and overview

Tuberculosis was a major contributor to mortality in Europe in the 18th century and is estimated to have caused 1,000 deaths per 100,000 people.[15] The BCG vaccine was developed in the 1910s to prevent tuberculosis and was administered to the first child in 1921.[16] BCG vaccination was scaled up widely in the 1940s across Europe. It became the main government strategy for containing tuberculosis and many high-income countries introduced national policies making BCG vaccination compulsory for all children.[17] As the incidence of tuberculosis declined to negligible levels, several high-income countries discontinued compulsory vaccinations. However, there has been continued and significant scientific interest in the *non-specific* effects of the BCG vaccine and whether it increases long-term survival beyond its effect on tuberculosis.

The proposed mechanism behind non-specific effects is that early BCG vaccination improves general childhood immunity, which may confer a lasting health impact as individuals age.[18,19] Despite the growing scientific interest over the past two decades, especially among laboratory scientists studying the cellular-level immune response to the vaccine, it is still inconclusive whether the early childhood improvement in immune response induced by the BCG vaccine has a causal impact on health in later life.[19,20]

There exists a small body of literature analyzing the relationship between the BCG vaccine and morbidity and mortality among adults.[21–29] Indeed, a recent study from Denmark suggests that children vaccinated with the BCG vaccine had a 42% lower hazard of mortality in adulthood.[27] If this association was evidence of a causal relationship, these results would have significant population policy implications and would suggest that re-introducing BCG vaccination in national vaccination plans, even in the absence of tuberculosis, may be a cost-effective and easy-to-implement way of improving long-term survival. However, this and the other existing studies on the BCG vaccine's non-specific effects are either based on small non-representative samples, limited to specific health outcomes rather than an overall measure like all-cause mortality, and most fundamentally are based on study designs that suffer from confounding. Thus, it is unclear whether the association between BCG and later-life survival is due to the causal effect of improved childhood immunity from vaccination or reflects the unobserved characteristics of the families and children that opted for or against the vaccine. To my knowledge, there is no causal evidence on the non-specific effects of the vaccine on survival into adulthood at the population level.

In my dissertation, I address these three key limitations. First, rather than rely on small or potentially non-representative samples, I use population data on all births and deaths in Sweden for birth cohorts born between 1950 and 1988. Second, rather than focus on specific health conditions, I examine the effects of BCG vaccination on cohort survival to age 30 based on all-cause mortality. Lastly, I employ three causal inference study designs – the RDD, the RKD, and the multi-period DiD model – to address the potential issues of confounding present in prior studies. I do not find that the BCG vaccine had non-specific effects on survival to age 30 in Sweden. This conclusion is consistent across analysis approaches and robust to several sensitivity analyses and alternate specifications. While BCG vaccination in the absence of tuberculosis might still be important for specific subpopulations, my results do not provide evidence in support of broad population policies to re-introduce BCG vaccination in high-income countries with a low burden of tuberculosis.

2.2 Background

Epidemiology of tuberculosis

Tuberculosis is an infectious disease caused by the mycobacterium tuberculosis bacterium that mostly affects the lungs but can also spread to other organs or the bones.[30] Tuberculosis is highly fatal if untreated but can be treated with a six-month antibiotic drug regimen. It is transmitted through the air (e.g. from talking or coughing) and is more likely to be observed among adults, males, and individuals who are immunocompromised (e.g. living with the human immunodeficiency virus), live with diabetes, are undernourished, or use alcohol or tobacco.[31]

The mycobacterium tuberculosis has been around for thousands of years but tuberculosis prevalence increased to an epidemic level only in the 18th century, reaching an estimated death rate of 1,000 per 100,000 inhabitants in 1800.[15,32–34] This dramatic increase in tuberculosis mortality is thought to be related to increasing urbanization leading to the close agglomeration of individuals in cities and poor living standards.[31] In the 19th century, the tuberculosis prevalence declined in high-income countries.[35] While, as of 2020, tuberculosis remains the second highest cause of death from infectious diseases globally, after COVID-19, the disease burden is concentrated in low-income and middle-income countries, with high-income countries only accounting for 2% of all recorded tuberculosis cases.[36]

Development and introduction of the BCG vaccine in Europe

The BCG vaccine is a live vaccine and was introduced in the 1920s.[16] Since then it has become one of the most widely used vaccines globally.[16,37] Several strains of the BCG vaccine emerged from the original strain isolated by Albert Calmette and Camille Guérin in 1908.[16] There is conflicting evidence on the vaccine's effectiveness and to date, it is poorly understood how it affects the immune system and why there is such a wide variation in the body's immunological response.[19] While the evidence is mixed, it is generally believed that the BCG vaccine only protects against the development of active tuberculosis but not infection itself, and that the vaccine has the greatest benefits when administered after birth rather than to adolescents or adults.[38,39] The BCG vaccine is safe for healthy children but poses a threat to immunodeficient ones, who can develop a disseminated BCG infection.[40] This fact is important for deciding which children should be given the BCG vaccination, a point which I will return to later on when discussing potential issues of confounding in prior research.

In Europe, the BCG vaccine was widely adopted in the 1940s.[16] In the large majority of countries it was administered right after birth.[17] While some countries, such as Sweden and Norway, made the BCG vaccination compulsory, other countries adopted policies that targeted high-risk groups only, such as healthcare workers or children of parents born in high-incidence countries. In the decades after the introduction of the BCG vaccine, the tuberculosis incidence continued to decrease dramatically in Western Europe and other high-income countries.[41] This decline led most governments of countries where vaccination was compulsory to discontinue their policies.[42] In Sweden, for example, tuberculosis mortality decreased from around 22 per 100,000 in 1950 to less than 4 per 100,000 in 1975.[43,44] In Norway, the country I used as counterfactual in one of the analyses, mortality attributable to tuberculosis was 29 per 100,000 in 1950 and decreased to 2 per 100,000 in 1975[a].[47] It remains unclear how much the BCG vaccine contributed to the decline in tuberculosis prevalence, or whether this decline was mainly due to improved living standards and nutrition.[35]

In Sweden, the country I study here, compulsory vaccination of neonates was introduced in 1940 and then reversed in April 1975 because of the persistently low tuberculosis prevalence.[17,48,49] Thus, children born in 1976 were the first birth cohort in which no newborn received the routine BCG vaccine. This shift was abrupt: vaccine coverage dropped from 95% to 2% in the years following its discontinuation.[50] Coverage then gradually increased to 13% in the cohort born in 1989 and covered at-risk groups such as children born to parents from high tuberculosis prevalence countries.[49] In Norway, BCG vaccination became compulsory in 1947 for students leaving elementary school, usually at age 13.[51] Mass vaccination campaigns started in 1947.[52] However, unlike Sweden, mandatory vaccination in Norway remained in

[a] To my knowledge, no data on the tuberculosis related mortality rate are available. Thus, I used the absolute numbers of tuberculosis deaths and divided them by the population size (in 100,000s) in the respective year.[45,46].

place until 2005, when the policy changed to a voluntary scheme. Recommendations were again updated in 2009 and since then vaccinations are limited to at-risk groups only.[53,54] BCG vaccine coverage in Norway increased from 88.6% among adolescents aged 13 in 1959 to 92.2% in 1973 and was above 97% between 1975 and 1998.[52,55]

Non-specific effects of the BCG vaccine

Non-specific effects are health effects of a vaccine that are unrelated to the targeted disease. The first non-specific effects were reported on the vaccinia vaccine against smallpox, which also seemed to protect against measles and other infectious diseases.[56] These findings led to the assumption that other live vaccines, such as the BCG vaccine, might have positive non-specific effects, too.[57] It is not entirely clear through which channels the BCG vaccine could provide protection against other diseases. There is evidence that the BCG vaccine causes an adaption of the innate, or unspecific, immunity, which is the fraction of the immune system humans have from birth on and is, thus, not induced in response to specific diseases through infection or vaccination.[58] This trained immunity, i.e. the change in the innate immunity after BCG vaccination, is one of the potential channels for BCG vaccine-related non-specific effects.[59] Today, the BCG vaccine is widely applied as a treatment for bladder cancer and research on its effectiveness in the treatment of other cancers is ongoing.[60]

Existing evidence of non-specific BCG effects

There is a small number of studies, most of them observational, estimating non-specific effects of the BCG vaccine on child survival.[61–72] The majority of these studies was conducted in low-income and middle-income countries and suggest a positive association between BCG vaccination and child survival. Evidence on the vaccine's non-specific effect on adult

morbidity and mortality is also limited.[21–29] All studies but one[27] are based on small non-representative samples or are limited to specific health outcomes. Most importantly, all studies except for one clinical trial[21] do not sufficiently account for potential confounding and can, thus, only estimate associations but not establish causal relationships.

For example, Pfahlberg et al. (2002) study the relationship between BCG vaccination and malignant melanoma among 1,230 individuals from eleven health centers in seven European countries between 1994 and 1997.[24] Using a case-control design, the authors compared those that did and did not receive the BCG vaccine and concluded that the BCG vaccine might reduce the risk of malignant melanoma. In contrast, Riekmann et al. (2019) linked data on 5,090 adults from the Copenhagen School Health Records to the Danish Cancer Registry and found no association between BCG vaccination and malignant melanoma.[25] Focusing on lymphoma and leukemia, Villumsen et al. (2009) used the same two data sources and found that individuals who had received the BCG vaccine during childhood had half the risk of developing lymphoma compared to those who had not.[29] There was no difference in the risk of developing leukemia.

Two observational studies estimated the association between BCG vaccination and adult survival. Kölmel et al. (2005) analyzed the association between the vaccinia and BCG vaccines and survival among individuals with malignant melanoma in six European countries and Israel.[22] The authors compared participants who had received the vaccine during childhood to those who had not and found no evidence of an association between BCG vaccination and survival. The only study analyzing the relationship between the BCG vaccination and long-term survival drew on the Copenhagen School Health Records Register used as part of the prior mentioned studies from Denmark. Rieckmann et al. (2017) linked these data to the Civil

Registration System and the Danish Register of Causes of Death databases, focusing on death by natural causes (excluding tuberculosis or smallpox).[27] Comparing those that did receive the BCG vaccine during childhood to those that did not, they found that vaccinated individuals had approximately half the risk of dying from natural causes than unvaccinated individuals.

While some of these studies suggest that the BCG vaccine has non-specific effects on morbidity and mortality, none of the study designs can establish a causal relationship[b] because they do not sufficiently account for confounding due to factors such as the healthy vaccinee bias.[69] The healthy vaccinee bias occurs if healthy children, and thus children with a higher overall probability of survival, are more likely to receive the vaccine than unhealthy children. The decision to not administer the vaccine can be based on concerns about side effects or because these parents have a lower health service uptake in general. Comparing vaccinated to unvaccinated individuals without considering systematic differences in characteristics that are correlated with the decision to vaccinate can result in an over- or underestimation of the vaccine's true non-specific effects. I address this evidence gap by applying three quasi-experimental methods that take advantage of the sudden discontinuation of the compulsory vaccination policy in Sweden to estimate the causal effect of BCG vaccination on survival into adulthood.

[b] Giamarellos-Bourboulis et al. (2020) conducted a clinical trial with 202 participants aged 65 years and older who either received the BCG vaccine or a placebo at hospital discharge. The trial shows that the short-term risk of infection was reduced in the treatment group. However, these results cannot be generalized to a broader population nor long-term survival.

2.3 Data and outcome construction

Data

I screened all available information on the BCG Atlas to identify countries that would be eligible for inclusion in this study.[17] First, I identified all countries which had a change in vaccination policy, moving from compulsory to optional vaccination as potential natural experiments. Next, I screened the documentation provided on each of these countries in the Human Mortality Database (HMD) as of January 19, 2022, to identify which of these countries have available data for all years in the study period.[73] I identified six potential countries with a change in vaccination policy that also had data available in the HMD (Austria, Denmark, Finland, France, Great Britain, Norway, and Sweden). I chose Sweden as most suitable for the following reasons: (1) there was a sharp discontinuation of compulsory vaccination in 1975 and BCG vaccine coverage dropped from 95% before 1975 to 2% in the years following the discontinuation;[50] and (2) among these six countries, Sweden was the first to abolish a nationwide policy and discontinue the BCG vaccine.[17] Thus, Sweden allows for the maximum observation period in terms of survival into adulthood.

One of the study designs, the multi-period DiD, additionally requires selecting a control country that followed a similar survival trajectory prior to the discontinuation of BCG vaccination but that did not discontinue the vaccine at the same or similar time as Sweden. Based on this criterion, I selected Norway as the most suitable counterfactual country for the DiD analysis[c]. For both Sweden and Norway, I accessed data on the number of births and age-

[c] If there were multiple suitable counterfactual countries, I could have combined them using a synthetic control approach. This was my initial intention after identifying seven potential control countries: Austria, Finland, France, Great Britain, Japan, Norway, and Portugal. Based on initial synthetic control analyses, I proceeded with the multi-period DiD rather than the synthetic control approach as no country other than Norway had a pre-trend that resembled Sweden, and as such the synthetic control approach gave nearly 100% of the weight to Norway.

specific death rates for each birth cohort from the HMD. To minimize confounding from the aftermath of World War II, I only included birth cohorts born in 1950 or later. Thus, the observation period covers cohorts born from 1950 to 1988, which allowed me to study the impact of BCG vaccination on the cohort probability of survival to age 30 (for those born in the final 1988 birth cohort, I had data on their survival up to the year 2018, when cohort members turned 30).

Outcome

The outcome of interest is the probability of survival to age 30 in each birth cohort by country. Constructing this outcome required information on the number of individuals that survived to age 30 in each cohort. The HMD data include cohort age-specific death rates but not the total number of deaths that occurred in a birth cohort by age. I, therefore, converted the age-specific death rates to death counts. I did this through the following procedure. First, I converted the cohort age-specific mortality rates to the age-specific probabilities of survival using the standard life-table approach.[74] Second, I set up a dataset with the number of observations equal to the number of births in a cohort. I then generated a variable for "alive at age 30" and used the cohort life table probability of survival from birth to age 30 to determine what share of this initial birth cohort survived to age 30, and correspondingly assigned values to the "alive at age 30" variable. For example, if among the 115,414 births for the 1950 birth cohort, the cohort-life table probability of survival to age 30 was 90%, I would assign values of 1 for "alive at age 30" to (0.9 x 115,414 =) 100,273 observations. This procedure was repeated for each birth cohort, resulting in a final dataset of 4,152,211 observations, which equals the total number of births in Sweden from 1950 to 1988. I repeated this approach to generate individual-level datasets for Norway as well as separately for males and females in each country.

2.4 Methodology

2.4.1 Regression Discontinuity Design: Theory

The RDD estimates the causal effect of an intervention or policy in situations where exposure to the intervention or policy is based on whether individuals fall on one side or another of some type of cut-off. This cut-off point is usually referred to as the "threshold" and the continuous variable on which the threshold is based is known as the "running variable." For example, individuals may be eligible for free health care (the policy) based on whether their income (the running variable) is below the poverty line (the threshold). In such circumstances, the RDD estimates the causal effect of the policy under the assumption that in the absence of the treatment, the relationship between the running variable and an outcome would have evolved continuously. Heuristically, this can be expressed that those just below the threshold are, on average, identical in all characteristics to those just above the threshold. The only difference is that those above the threshold receive the treatment. By construction, the RDD estimates the local average treatment effect (LATE) at the threshold value.

The RDD has three main assumptions:

> Assumption 1: The probability of receiving the intervention changes discontinuously at the threshold.
>
> Assumption 2: The outcome would be continuous at the threshold in the absence of the intervention.

Assumption 3: Individuals should not systematically sort around the threshold with the aim to obtain or avoid the intervention.

Whether these three assumptions can be considered fulfilled in the context of the two studies is elaborated on in Sections 2.4.2 and 3.4.

I followed the continuity-based RDD approach described by Cattaneo et al. (2019).[75] This includes using a local linear model, including triangular Kernel weights (to give more weight to observations closer to the threshold), and the mean squared error (MSE) optimal bandwidth (a data-driven approach for determining the bandwidth around the threshold, which removes arbitrary bandwidth selection and potential manipulation of the bandwidth size by researchers).[76] For inference, I used robust bias-corrected standard errors and confidence intervals.[75] The general RDD estimation model is set up as follows:

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 D_i + \beta_3 X_i D_i + \varepsilon_i \quad (1)$$

Y_i is the outcome of individual i, X_i is the continuous running variable based on which the intervention is allocated, and D_i is a binary indicator that takes the value 1 if an individual received the intervention.[12] β_2 is the causal effect of the intervention on the outcome for individuals at the threshold.

2.4.2 Regression Discontinuity Design model estimation

Equation (1)

In the BCG study in equation (1), Y_i is the survival status at age 30 for individual i, X_i is a continuous measure of year of birth (the running variable), and D_i is a binary indicator that takes the value 1 if an individual was born after the discontinuation of the mandatory BCG vaccination. β_2 is the causal effect of the discontinuation of the BCG vaccine on survival to age 30 for the cohort born in the threshold year, i.e. 1976. For the female sample, the local linear trend did not model well the data within the bandwidth. For this reason, I used a local quadratic trend.

Assumption 1: Discontinuous change in the probability of receiving the intervention at the threshold

The running variable X_i is year of birth and the threshold is 1976, the birth year of the first cohort for which the BCG vaccine was not mandatory anymore. There are no yearly data on BCG coverage for the years around the threshold. However, Romanus et al. (2006) report that BCG vaccine coverage dropped from 95% to 2% in the five years following the discontinuation, which indicated that the probability of receiving the BCG vaccine decreased sharply. This evidence supports Assumption 1.

Assumption 2: Continuity of the outcome at the threshold in the absence of the intervention

This assumption requires that there was no substantial change in the probability of survival to age 30 induced by an event other than the BCG vaccination discontinuation. To my knowledge, there have been no major shifts in policies or national-level events, such as natural disasters, which could have affected the probability of survival of the cohorts born just before the

discontinuation differently from those born just after. Thus, it is plausible that Assumption 2 is fulfilled.

Assumption 3: No systematic sorting around threshold

I assess this risk of systematic sorting around the threshold to be negligible in the context of this study as I consider it unlikely that parents accurately anticipated and based their family planning on the future BCG policy change. This is supported by the data, which shows no clustering of births either above or below the threshold (Figure S1). Assumption 3 is, thus, considered to be fulfilled.

2.4.3 Regression Kink Design

The RDD estimates whether there was a sudden change in the level of the probability of survival after the BCG vaccine discontinuation. It could, however, also be the case that the discontinuation slowed down the rate of change in the probability of survival to age 30. To investigate this, I applied the RKD.[12] The RKD relies on the same assumptions as the RDD but is applied when there is not a discontinuity in the probability of being treated but in its first derivative, i.e. in the slope of the relationship between the treatment and the assignment variable at the threshold. In the context of this analysis, this would be the case if the probability of receiving the vaccine was still high in 1975, the year of the discontinuation, and only gradually decreased in the following years. Another potential scenario could be that the probability of being vaccinated already declined before the official discontinuation and this decline either slowed down or sped up after the discontinuation. Rather than causing a sudden shift in the level of the probability of survival, the gradual discontinuation would cause a change in its slope at the threshold.

As in the RDD, the model included triangular kernel weights, the MSE optimal bandwidth, and robust bias-corrected standard errors and confidence intervals. Different from the RDD, the model included a local quadratic trend.[77]

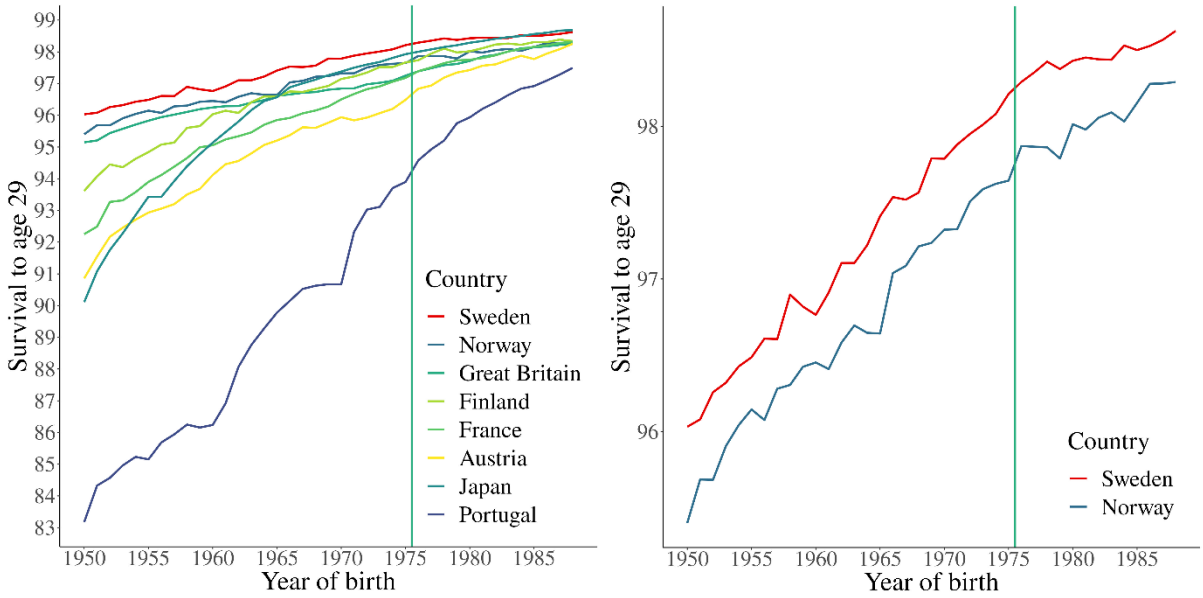
2.4.4 Multi-period Difference-in-Differences

While the RDD and the RKD estimate the effect of the BCG discontinuation for the cohort born in the threshold year, it could be the case that the effect only emerged after several birth cohorts (for example if it took a few birth cohorts to fully discontinue the vaccine). To investigate the effect of BCG vaccination in the case of this scenario, I conducted a multi-period DiD model (sometimes also referred to as leads and lags model) with Norway as the counterfactual.

The multi-period DiD estimates the effect of the vaccine discontinuation by comparing the probability of survival in Sweden and Norway in each birth cohort accounting for temporal trends, i.e. the general positive trend in the probability of survival, and the baseline difference between the two countries. The central identifying assumption of the multi-period DiD is that in the absence of BCG discontinuation, the cohort probability of survival to age 30 in Sweden would follow the same trend as the cohort probability of survival to age 30 in Norway (the so-called parallel trends assumption). This assumption is commonly assessed by comparing the trends in the outcome variable in the pre-intervention period. While I formally assess this assumption later, the visual evidence presented in Figure 1 shows that among several potential comparison countries, the cohort mortality trend in Norway most closely mirrored Sweden's. By estimating the effect of the BCG discontinuation on survival for multiple birth cohorts born

after the discontinuation – and not just the 1976 birth cohort as in the RDD and RKD - this approach reveals whether the effect wanes or intensifies over time or whether there is a lag in the effect and only cohorts born some years after the discontinuation are affected.

Figure 1: Survival to age 29 in Sweden and potential control countries



Note: I plotted the probability of survival to age 29, rather than 30, because data needed to construct survival to age 30 were not available for France and Great Britain. The vertical line divides the birth cohorts into those born before the vaccine discontinuation (1975 and earlier) and those born after. The left panel shows the probability of survival for Sweden and each potential control country. The right panel zooms in and only displays the probability of survival in Sweden and Norway.

The multi-period DiD regression model is set up as follows:

$$Y_{ict} = \beta_0 + \beta_1 \mu_c + \boldsymbol{\beta_2 \lambda_t} + \boldsymbol{\beta_3 \mu_c \lambda_t} + \varepsilon_{ict} \quad (2)$$

with i indexing individuals, *c* indexing countries and *t* indexing years.[12] μ_c is a country dummy that accounts for the baseline difference in the probability of survival between the treatment (Sweden) and counterfactual (Norway) countries. λ_t is a vector of year dummies that account

for the time trend common to both countries (1975, the year of the BCG vaccine discontinuation, is the reference year). μ_t λ_t is the interaction between the country and year dummies for each of the birth cohorts. The coefficients of the country-year interaction terms (β_3) for cohorts born before 1975 provide a test of the parallel trends assumption (these coefficients should be not statistically significantly different from zero). The coefficients in β_3 for cohorts born after 1975 represent the effect estimates. Lastly, rather than estimate treatment effects for each birth cohort born after the BCG discontinuation, I also estimated a common treatment effect for all post-discontinuation birth cohorts (β_3) by interacting the country dummy (μ_c) with a post dummy (*Post*=1 for all cohorts born in or after the year of discontinuation) and including year fixed effects (λ_t) as dummy variables:[78]

$$Y_{ic} = \beta_0 + \beta_1\mu_c + \boldsymbol{\beta_2\lambda_t} + \beta_3\mu_c * Post + \beta_4 Post + \varepsilon_{ict} \quad (3)$$

Heterogeneity analysis

I estimated the RDD, RKD, and DiD models using data on the total population born between 1950 and 1988 in Sweden. To test whether the non-specific effects of the BCG vaccine differed by sex, I additionally ran the analysis separately for males and females.

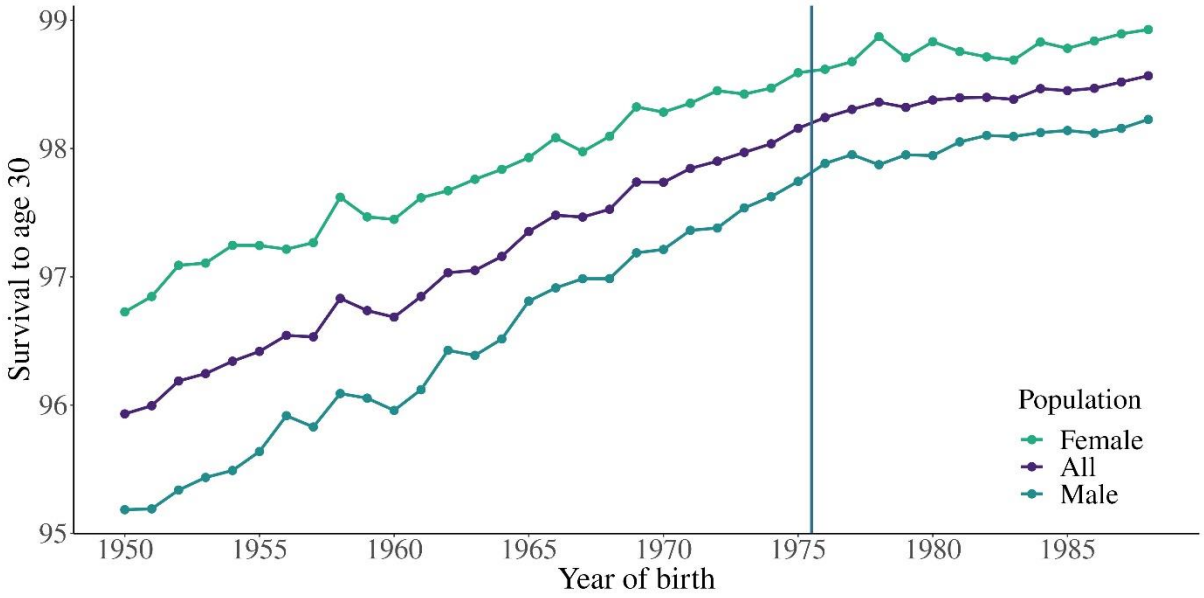
2.5 Results

2.5.1 Sample description

The final data include one observation per person born from 1950 to 1988. For Sweden, this includes 4,152,211 individuals in total (2,137,830 males and 2,014,381 females), ranging from 91,780 in the cohort born in 1983 to 123,354 in 1966. In Norway, 2,326,387 people were born in this period (1,196,500 males and 1,129,887 females), ranging from 49,937 in 1983 to 67,746

in 1969. Figure 2 shows the probability of survival to age 30 in Sweden for birth cohorts born between 1950 to 1988. Survival to age 30 increased from 95.9% in the 1950 birth cohort to 98.6% in the 1988 birth cohort. Across all years, the probability of survival was higher among females than males. For example, in 1975 the probability of survival to age 30 was 98.6% among females and 97.7% among males. Despite this difference in the absolute level, survival in the female and male subpopulations followed a similar trend. Visually, there was no evidence of an abrupt change in the probability of survival in the entire population when comparing the cohort born in the year of the BCG vaccine discontinuation (98.16% in 1975) and the first cohort for whom the vaccine was optional (98.24% in 1976). This smooth trend around 1975-1976 was also present when looking at males and females separately.

Figure 2: Cohort survival from birth to age 30 in Sweden



Note: The vertical line divides the birth cohorts into those born in or before the year of the vaccine discontinuation (1975 and earlier) and those born after (1976 or later).

2.5.2 Regression Discontinuity Design results

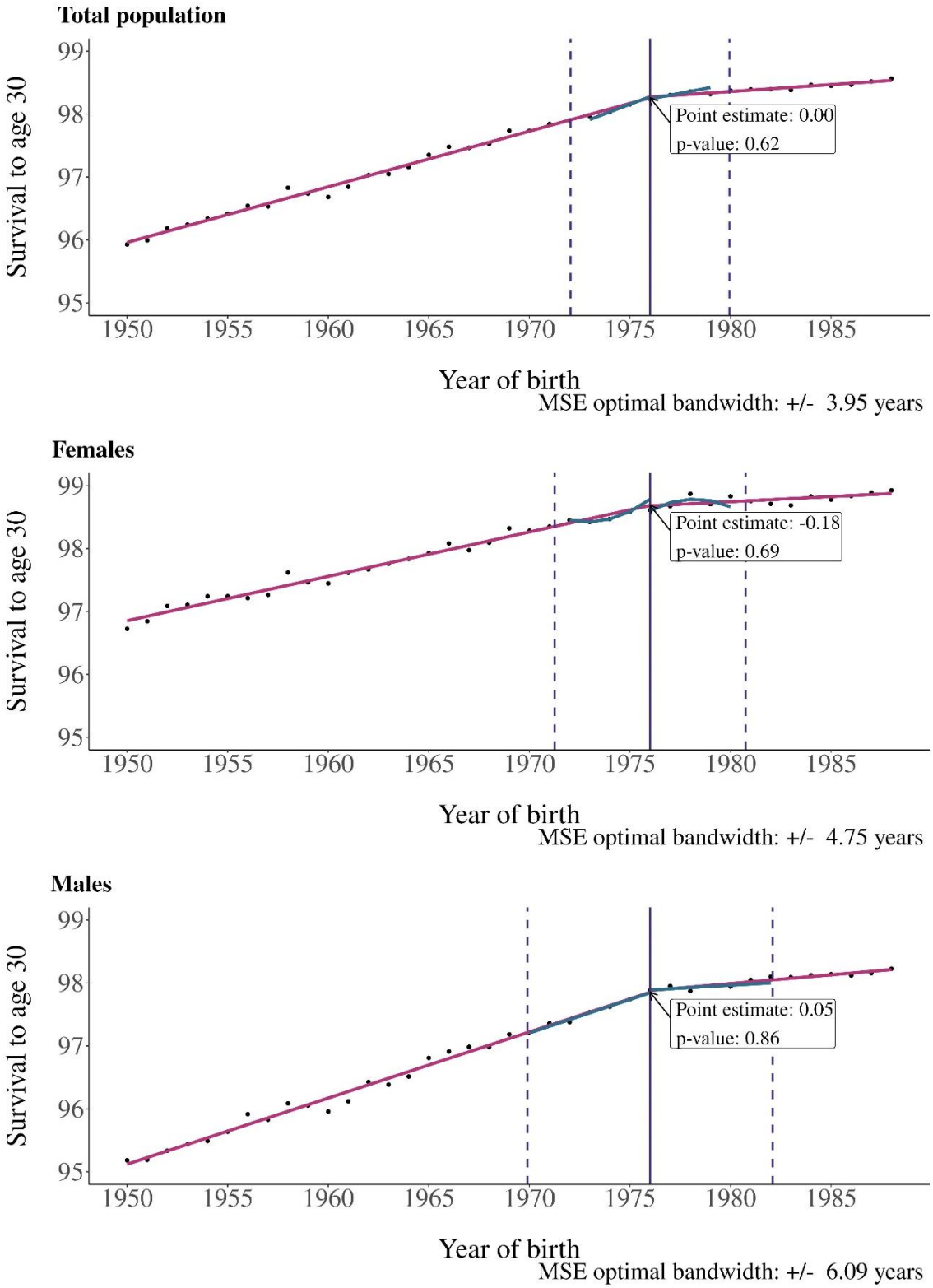
The RDD analysis confirms the results of the visual inspection: I do not find evidence of an effect of the BCG vaccination discontinuation on survival into adulthood in the birth cohort born in 1976. I estimated a precise null effect (0.00 percentage points (pp) (95% CI -0.46 - 0.27)) on the probability of survival to age 30 at the point of BCG vaccination discontinuation (Table 2, Figure 3). As with the visual results, this finding was not driven by just females or males. I find no evidence that BCG vaccine discontinuation affected the probability of survival to age 30 among females (-0.18pp (-1.05 - 0.70)) or males (0.05pp (-0.26 - 0.32)) (Table 2, Figure 3).

Table 2: Regression Discontinuity Design estimation results, threshold year 1976

	Total	Females	Males
Estimation results			
Coefficient	0.00	-0.18	0.05
p-value	0.62	0.69	0.86
95% CI	(-0.46 - 0.27)	(-1.05 - 0.70)	(-0.26 - 0.32)
Bandwidth details			
Bandwidth	3.95	2.87	6.09
N (within bandwidth)	707,074	445,072	682,818

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). For the female subsample, the model included a local quadratic trend as the local linear trend did not fit the data structure. The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The table displays the local average treatment effect for the birth cohort of 1976 and confidence intervals resulting from robust bias-corrected standard errors.
Abbreviation: CI = confidence interval

Figure 3: Non-specific effects of the BCG vaccine discontinuation on cohort survival from birth to age 30 in Sweden



Notes: Pink lines represent linear trends fitted separately for cohorts born before and after the vaccine discontinuation; blue lines are local linear trends (local quadratic trend for females) fitted within the bandwidth and separately for cohorts born before and after vaccine discontinuation; dashed lines represent the mean squared error optimal bandwidth; the purple vertical line is set at the year 1976, year of birth of the cohort for whom the local average treatment effect was estimated.

2.5.3 Regression Kink Design results

The RKD results show no evidence of an effect of the BCG vaccine discontinuation on the rate of change in the probability of survival to age 30 in the three population groups (Table 3). All point estimates were marginally small and confidence intervals overlapped with zero. In the total population, the effect estimate was -0.09pp (-1.26 - 0.88), in the female population -0.10pp (-1.45 - 1.26), and in the male population -0.08pp (-1.89 - 1.39). This indicates that even if the discontinuation of the BCG vaccine was not sharp but the rate of decline in the vaccine coverage changed at the threshold, the BCG vaccine did not have non-specific effects on survival to age 30.

Table 3: Regression Kink Design estimation results, threshold year 1976

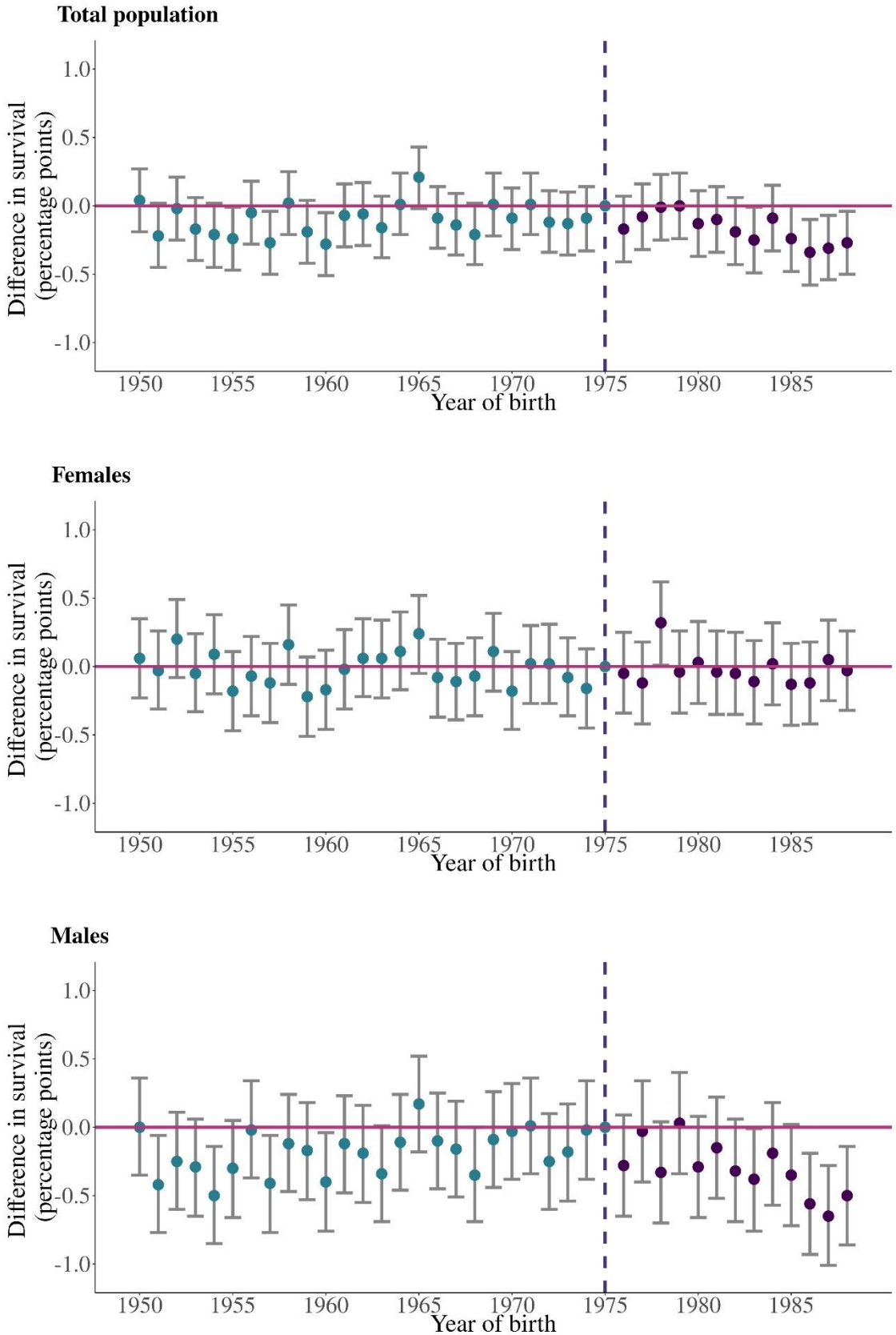
	Total	Females	Males
Estimation results			
Coefficient	-0.09	-0.10	-0.08
p-value	0.73	0.89	0.77
95% CI	(-1.26 - 0.88)	(-1.45 - 1.26)	(-1.89 - 1.39)
Bandwidth details			
Bandwidth	5.00	4.76	4.30
N (within bandwidth)	916,411	445,072	471,339

Note: The model estimation included a local quadratic trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The precise bandwidth in the total population is 4.9996, with a floor of 4. The table displays the local average treatment effect for the birth cohort of 1976 and confidence intervals resulting from robust bias-corrected standard errors.
Abbreviation: CI = confidence interval

2.5.4 Multi-period Difference-in-Differences results

While the RDD and RKD estimate potential non-specific effects for the cohort born in the year of the vaccine discontinuation, the multi-period DiD allows to generate estimates for each birth cohort and, thus, yields the opportunity to detect lagged effects. The event-study plot in Figure 4 shows the difference in survival between birth cohorts born in Norway and Sweden for each cohort born before and after the BCG discontinuation. The coefficients are shown net of an overall level difference in survival between the two countries and a time trend. In support of the parallel trends assumption, I find that most point estimates in the pre-discontinuation period were not statistically different from zero (exact values are shown in Table S1). This suggests that prior to the discontinuation of the BCG vaccination in Sweden, both countries followed a parallel trend in cohort survival to age 30. The coefficients on the right side of the vertical line in 1975 capture the non-specific effect of BCG discontinuation on survival in Sweden. Similar to the RDD and RKD results, I find no evidence of differences in cohort survival to age 30 in the post-BCG-discontinuation period between individuals born in Sweden and Norway across most birth cohorts. For Swedish cohorts born after 1986, the probability of survival to age 30 seemed to have been lower. However, these differences are for cohorts born 10 years after the discontinuation of the BCG vaccine. For this reason, I consider it more likely that the negative point estimates for younger birth cohorts were caused by other changes at the population level that differed between Norway and Sweden at that time rather than being caused by the discontinuation of the BCG vaccine.

Figure 4: Event study plot displaying multi-period Difference-in-Differences results



Note: Coefficients (with 95% confidence intervals) display the difference in the probability of survival between cohorts born in the respective year in Sweden and Norway net the secular time trend and fixed country differences. The dashed vertical line marks the reference group, which is the cohort born in 1975.

By splitting the results by birth cohort, the event-study may result in underpowered estimates of the effect of the BCG discontinuation. When pooling all data from the pre- and post-discontinuation periods, respectively, I find a very small negative, significant (based on the p-value) effect of the BCG vaccine on the probability of survival to age 30 by -0.06pp (-0.11 - 0.00) (Table 4). While this result is statistically precise due to the large sample size (over six million observations), the estimated effect was extremely small in magnitude at less than a 10th of a percentage point and thus of minimal policy significance.

Table 4: Pooled Difference-in-Differences estimation results, reference year 1975

	Total	Females	Males
All observations			
Coefficient	-0.06	0.00	-0.11
p-value	0.04	0.91	0.02
95% CI	(-0.11 - 0.00)	(-0.07 - 0.07)	(-0.19 - -0.02)
Within bandwidth			
Coefficient	0.05	0.07	-0.05
p-value	0.39	0.26	0.40
95% CI	(-0.06 - 0.16)	(-0.05 - 0.19)	(-0.18 - 0.07)

Note: I pooled data from all pre-discontinuation and post-discontinuation years respectively. Regression models include year dummies. The mean squared error optimal bandwidth was 3 for the full population, 2 for the female population, and 6 for the male population. The reference year was 1975.

I draw a similar set of conclusions when examining females and males separately. Among both the female and male populations, there was no difference in the probability of survival for the cohorts born before the BCG vaccine discontinuation, indicating support for the parallel trend assumption (Figure 4, Table S1). In the female subpopulation, there was also no difference in the probability of survival between Sweden and Norway after the vaccine discontinuation (net of the time and level trends). This cohort-level finding was confirmed in the pooled analysis

(0.00pp (-0.07 - 0.07), Table 4). In the male subpopulation, the results of the cohort-level multi-period DiD also suggest that there was no non-specific effect of the BCG vaccine on survival (Figure 4, Table S1). However, as observed in the total population, cohorts born in 1986 or later had a lower probability of survival in Sweden than in Norway. Pooling all pre- and post-discontinuation birth cohorts reveals that the probability of survival decreased by 0.11pp (-0.19 - -0.02) among males (Table 4).

It is possible that the significant results in the total and male populations were driven by the youngest birth cohorts, which represent approximately one fourth of the post-discontinuation birth cohorts, but were born 10 years after the vaccine discontinuation and thus the validity of the DiD assumption that any difference was due to the discontinuation alone for this group is questionable. To investigate this, I restricted the sample to the cohorts born within the MSE optional bandwidth defined in the RDD analysis. The results show that for the birth cohorts born within the MSE optimal bandwidth, there was no difference in the probability of survival between the total, male, and female populations in Sweden and Norway (Table 4).

2.5.5 Sensitivity analyses

I conducted several sensitivity analyses to test the robustness of my results. First, it could be the case that the rate of change of survival across cohorts depends on the absolute level of survival and that this functional form affects the estimates. To investigate this, I plotted the log probability of survival and found that the flattening of the cohort survival trends was not driven by the fact that the probability of survival approached 100% (Figure S2). Second, in 1975 more individuals were born after the discontinuation on April 1 than in the first three months of the year.[79] To account for this, I set the threshold to be one year earlier (1975 in the RDD and

RKD, and 1974 in the multi-period DiD), which produced consistent results with those of the main analysis (Tables S2 to S4, Figure S3). Third, in the RDD analysis, the point estimate and inference might depend on the bandwidth within which the LATE is estimated. Increasing the bandwidth will reduce variance as more observations are included in the analysis. However, it increases the bias because these observations are less similar to each other than those closer to the threshold. Decreasing the bandwidth would have the opposite effect and increase variance while reducing the bias. It was not possible to decrease the bandwidth due to the limited number of mass points in my analysis but increasing the bandwidth by one, two, and three years, did not change the results and all point estimates remained statistically insignificant (Tables S5 and S6).

2.6 Discussion

There is continued interest in the non-specific effect of the BCG vaccine and whether populations should be vaccinated even if there is a low burden of tuberculosis.[20] If the BCG vaccine had non-specific effects and increased survival into adulthood among the general population, it could be a simple and cost-effective intervention to improve population health. Mechanistically, such an effect seems plausible since the BCG vaccine is thought to improve general childhood immunity.[18] Using population data and three complementary quasi-experimental methods that take advantage of the sudden discontinuation of the mandatory BCG vaccination in Sweden, I find no evidence for non-specific effects of the BCG vaccine on the probability of survival to age 30. In other words, up to this age and at the population level, the BCG vaccine did not appear to have substantial protective effects against mortality from diseases other than tuberculosis. This result was robust to multiple sensitivity and robustness

checks and remained valid when estimating the effect separately for the male and female subpopulations.

These findings are in stark contrast to a previous study from Copenhagen, Denmark, which estimated that BCG vaccination was associated with a 42% higher probability of survival.[27] The differences between our studies are likely due to residual confounding. In particular, the authors compare children that did and did not receive the vaccination during a period in Denmark when BCG vaccination became voluntary. Thus, parents self-selected their children for vaccination, and it is likely that the decision to vaccinate is related to characteristics that also influence the probability of survival. Such factors could include parental knowledge about the health of their child (as mentioned previously, BCG vaccination can have strong side effects for children with existing preconditions) and the background and socioeconomic status of parents who decide to vaccinate their children compared to those who do not. The authors of the Denmark study undertook several steps to adjust for such potential sources of confounding. Nevertheless, there is still a likelihood that the results were driven by unobserved systematic differences between the vaccinated and unvaccinated that affected both the vaccination status and survival since vaccination status was related to a direct parental choice and not a mandatory law as in my study.

The currently unknown potential for non-specific effects among some sub-populations raises the question of whether vaccinating an entire population would provide a cost-effective way of realizing all potential non-specific effects without having to target specific population groups. Such an approach would come with trade-offs. First, the intensity of the non-specific effects will depend on when the vaccine is administered. For example, Giaramellos-Bourboulis et al.

(2020) show that the BCG vaccine, if given just before hospital discharge, increased the time to first infection among the elderly. This non-specific effect may not have materialized if the vaccine had been given during childhood because adaptions in the innate immune system are likely only transitory.[80] Thus, to reap all non-specific benefits, the population would have to be revaccinated at regular intervals. Second, the BCG vaccine is cost-effective against tuberculosis under standard thresholds. However, given the lack of a detectable population-level non-specific effect, it is unlikely to be cost-effective when the objective is to improve population survival in a setting like Sweden. Third, the BCG vaccine can have non-negligible side effects. While the most common side effects are mild and temporary (fever, headache, or soreness in the location where the vaccine was given), less common and more severe side effects are abscesses, bone inflammation, or disseminated tuberculosis.[30] The latter is a particular risk for immunocompromised individuals. Taken together, while BCG vaccination may protect sub-populations, a broad population policy of continued vaccination is unlikely to meet conventional cost-effectiveness thresholds and comes with the risk of potentially serious side effects among individuals with a low expected benefit.

One important consideration is that my results are for Sweden, a country with a nearly negligible burden of tuberculosis and where infectious disease mortality, excluding deaths from Covid-19, is extremely low.[81] The lack of a strong relationship between early childhood BCG vaccination and adult mortality in this context is not necessarily evidence that changes to early life immunity do not affect adult mortality risk, but rather that such life-course effects may become less important as the general level of infectious mortality in a population decreases. BCG vaccination may have beneficial non-specific effects for individuals at elevated risk of mortality from infectious diseases, such as those in many low-income and middle-income countries, or for specific at-risk groups within low tuberculosis prevalence countries.

Evaluating the non-specific effects of BCG vaccination among adults in such populations is an important area of future work. Furthermore, I was only able to observe survival to age 30. Due to the weakening of the immune system with increasing age, infectious diseases become more prevalent at older ages.[82] If the BCG vaccine protected against infectious diseases, non-specific effects might be observed among the elderly. However, estimating whether the BCG vaccine discontinuation affects survival into old ages in Sweden requires data following individuals up to these ages. These data will only become available over the next three to four decades, as individuals born just after the vaccine discontinuation age.

A second important consideration with RDD analyses is that the effect estimate of a treatment or policy applies only to those within the bandwidth around the threshold point. In the case of this study, the RDD estimates the effect of BCG discontinuation on the first birth cohort not receiving the vaccine. If the BCG vaccine protected against infectious diseases, in particular during childhood as suggested by previous studies, there might be a time lag between the discontinuation of the vaccine and the realization of the non-specific effects as younger cohorts become exposed to larger shares of unvaccinated individuals.[21,61] In this case, cohorts born after infectious diseases have crossed a critical prevalence threshold would be affected by the BCG discontinuation whereas those born during or just after the discontinuation would not. Another reason for lagged effects would be a gradual decrease in the BCG coverage over several birth cohorts rather than an abrupt change. However, both these scenarios would be captured in the multi-period DiD analysis. Therefore, the null results in the RDD, RKD, and multi-period DiD suggest that there were no immediate nor lagged non-specific effects of the BCG vaccine.

This study has several limitations. If an exogenous factor, which I did not account for in the analysis, caused a decline (increase) in the probability of survival at the same time as the discontinuation of BCG vaccination, it could have offset potential beneficial (harmful) non-specific effects of the BCG vaccine. To rule this out, I undertook several steps. First, in the sensitivity analysis, I varied the threshold year. The conclusions of all three quasi-experimental method analyses remained unaffected by this change. Second, I conducted an extensive search to identify potential large-scale changes in the health, economic, and political sectors in Sweden and Norway. I found no evidence of any changes in the living situation in both countries, which could have differentially affected survival at the population level in either of the countries. The vaccinia vaccine was discontinued in Sweden in 1976, i.e. shortly after the BCG vaccine.[48] However, given the fact that this vaccine was discontinued around the same time in Norway and I also find no statistically significant effect in the multi-period DiD analysis, I do not expect the vaccinia discontinuation to have biased the results.[83] Because of data constraints, my analysis does not assess whether the BCG vaccine protects against COVID-19 because cohort death rates are only available up to 2018.

My study did not find any non-specific effects of the BCG vaccination on survival into adulthood in Sweden. Thus, my research suggests that re-introducing or continuing national mandatory BCG vaccination in countries with similar population mortality and morbidity profiles as Sweden is unlikely to lead to substantial or cost-effective improvements in population health.

3. The home-based screening study

3.1 Rationale and overview

Uncontrolled hypertension substantially increases the risk of developing cardiometabolic diseases (such as diabetes, heart attack, and stroke) and is the leading risk factor for cardiovascular disease mortality worldwide.[84] Therefore, controlling hypertension is a highly effective measure for reducing the risk of cardiometabolic diseases. Despite its importance, in many countries, including India, the prevalence of uncontrolled hypertension is high while rates of hypertension diagnosis and treatment are low. As of 2018, an estimated 46% of adults aged 45 or older in India had hypertension. Yet just 56% of these individuals were diagnosed and even fewer, 39%, took hypertension medication. Only 32% had their blood pressure under control, which indicates a severe lack of management of the disease.[85] Due to population aging, the number of people in need of hypertension care will increase in the future placing an increasing strain on the Indian health care system.[86]

To address the growing burden of hypertension and cardiometabolic diseases, the Indian government initiated "The National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke" in 2010 and the "National Multisectoral Action Plan for Prevention and Control of Common Non-Communicable Diseases 2017-2022" in 2013. [87,88] A key component of both plans is population- and community-based hypertension screening and several state governments have started to implement home-based screening initiatives.[88,89] The main theory of change behind such home-based screening efforts is that once individuals are made aware that they may have hypertension and are referred to the health system for follow-up, they will seek formal health care, become diagnosed, initiate treatment, and ultimately control their blood pressure. Yet the limited available evidence evaluating

home-based screening initiatives suggests that it has small or even null effects on blood pressure levels.[90–93] Reasons for these null effects could be that individuals do not see hypertension treatment as a pressing issue or that they might not have the financial or time resources to adhere to the treatment in the long term.[94–97] The lack of improvement in hypertension control might also be brought about by health care workers not prioritizing hypertension care because of a large number of clients with acute health issues or a shortage of material resources to initiate and treat people living with hypertension.[95,97] In Section 3.6 I discuss potential reasons why home-based screening might not improve hypertension care uptake and blood pressure control in more detail.

While informative, the existing evidence has two primary limitations, especially for informing policy in the Indian context. First, none of these studies used data from India limiting its generalizability to the Indian context. Second, although three of these four studies estimated the effect of home-based screening on blood pressure levels, they did not evaluate intermediate outcomes, such as hypertension diagnosis and treatment initiation, which are a prerequisite for achieving blood pressure control. To understand where governments should intensify their efforts and at what stage linkage to care fails, it is crucial to look at changes in preceding stages of the cascades of care including diagnosis and treatment. Previous evidence suggests that an individual's responsiveness to health information varies with their characteristics such as education, age, or an already existing linkage to the health system.[98] There is limited rigorous evidence on whether, to what extent, and which individuals act upon information received as part of home-based screening programs and which population groups benefit most from such initiatives.[90–93]

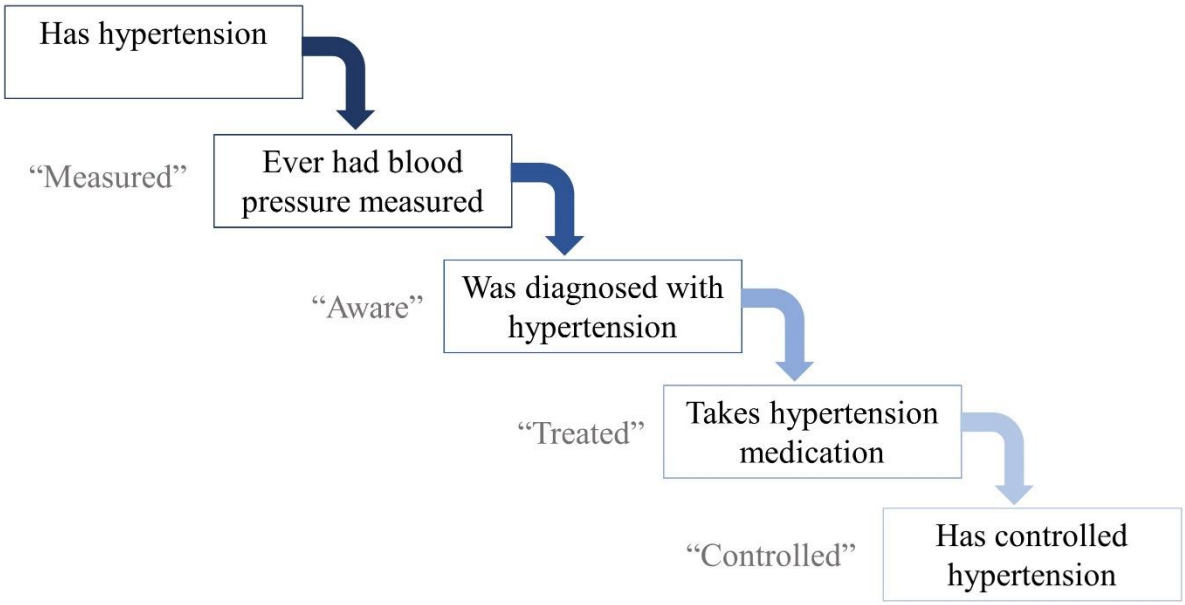
To my knowledge, no large-scale home-based hypertension screening initative in India has been evaluated to date. It remains unclear, whether the screening, coupled with a provision of health information on the need for hypertension control, actually leads to behavioral change and if so, among which population groups. In my dissertation, I aim to address this knowledge gap by using six waves of the Centre for Cardiometabolic Risk Reduction in South Asia Study conducted between 2010 and 2018. I estimate the causal effect of home-based hypertension screening on formal hypertension diagnosis and drug treatment in two large Indian cities (Chennai and Delhi). My study focuses on these two outcomes as this is where the majority of individuals with hypertension are lost in the progression through the cascades of care.[99,100] I employed the RDD and find that home-based screening did not lead to an increase in formal diagnosis or treatment within the 12 months following the blood pressure measurement and referral.

3.2 Background

Hypertension

Hypertension, commonly known as high blood pressure, is the main risk factor for cardiometabolic diseases, such as heart attacks, ischemic heart disease, and stroke. Since these diseases are major contributors to mortality in many countries, improving hypertension control has the potential for inducing large population health benefits. Hypertension can be treated with oral medication such as ACE inhibitors, calcium channel blockers, or angiotensin receptor blockers.[101] These drug treatments are affordable, cost-effective, and included in the World Health Organization's Best Buys to manage cardiovascular diseases.[2,102,103] Furthermore, this set of drugs typically has no or only mild side effects, is widely available, and dispensed free of charge in public health care facilities in India.[101,104]

Figure 5: Cascades of hypertension care



Note: Indicators for "measured", "aware", and "treated" are usually based on self-reported information. "Controlled" is based on blood pressure measurements.

Unmet need for hypertension care in India

Recent studies using data from India reveal a large unmet need for hypertension care and that the majority of individuals living with hypertension are not even aware that they have the condition. Lee et al. (2022) analyzed data from the nationally representative Longitudinal Ageing Study in India and estimated the individuals' progression through the cascades of care (Figure 5). The prevalence of hypertension was 46% among adults aged 45 years and older. Among those, 56% were "aware", 39% "treated", and 32% "controlled". Awareness and treatment increased with age, education, and household wealth and were higher among women and in urban areas. Other studies by Prenissl et al. (2019) and Amarchand et al. (2022) using different data sources from India had similar findings. Low rates of awareness of a hypertension diagnosis and current treatment were also observed across other low-income and middle-income countries worldwide.[105] These studies show that the largest loss in the cascades of care in these countries, including India, occurs at the second stage, i.e. individuals being aware of a hypertension diagnosis. Home-based screening has the potential to address this loss by

providing health information on hypertension and motivating individuals with high blood pressure to seek care.

Improving hypertension control in India

In 2010, the Indian government initiated the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS) with the objective to expand and improve diagnosis and treatment of several non-communicable diseases and their risk factors such as hypertension.[87] The NPCDCS strategic plan, implemented from 2012 to 2017, involved primary, secondary, and tertiary care and also community-based organizations and community health workers. The plan stipulates opportunistic screening for all individuals aged 30 years or older, which means that they should be screened for hypertension at every interaction with the health system. Successful implementation of this screening initiative on the ground would result in early detection and treatment of hypertension and over time lead to the completion of the first stage of the cascades of care ("screened") by all individuals aged 30 years and older. To date, there is limited published monitoring data on the NPCDCS implementation. In 2015 to 2016, 12.6 million individuals have been screened for diabetes and hypertension.[104] Furthermore, more than 6,000 facilities offering non-communicable disease care have been newly established across all states.[106] In 2013, to continue the progress in non-communicable disease prevention and control, the Indian government set up a follow-up strategic framework spanning the years 2017 to 2022: the "National Multisectoral Action Plan for Prevention and Control of Common Non-Communicable Diseases 2017-2022" (NMAP).[88] This action plan aims to increase the priority of non-communicable diseases in policy making, accommodate health promotion in a variety of settings, further strengthen the health system through capacity building and availability of more resources, and establish a monitoring and evaluation system.

State governments in India are increasingly interested in improving hypertension control through home visits. In Tamil Nadu, a state in Southern India, the state government introduced the community-level Makkalai Thedi Maruthuvam (MTM) scheme in August 2021 to improve non-communicable disease control.[107] The scheme involves home visits by professional and lay health care staff who screen individuals for several conditions, including hypertension. The health care staff measures the blood pressure of all adults aged 18 years and older and refers everyone with high blood pressure to a health care facility for formal diagnosis and, if required, treatment initiation. Under the MTM scheme, hypertension medication is delivered to the homes of adults aged 45 years or older. The estimated annual cost of the MTM scheme (including all components, not just hypertension health service provision) is 2,571,578,350 Rupees (approximately 31 million US dollars). The government expects the MTM to increase hypertension control from 7.3% to 10.3% over the course of four years.[108] While the government plans to monitor progress through the collection of individual-level data, no results on the first year of implementation have been published yet.

Evidence on the effect of home-based screening on hypertension control in low-income and middle-income countries

The main behavioral theory of change behind home-based screening is that once people are screened and educated about their blood pressure level and the importance of controlling blood pressure, they will take action and seek care. Yet several recent studies from other low-income and middle-income countries found that home-based screening did not necessarily translate into meaningful hypertension improvements. Chen et al. (2019) used data on adults aged 65 years or older living in 22 of China's 31 provinces. They estimated the effect of home-based screening on systolic and diastolic blood pressure levels by employing an RDD and found a reduction of 6.3 mmHg in the systolic blood pressure but no significant change in the diastolic

blood pressure. There was no heterogeneity in the effect across age, sex, education, and other socio-demographic characteristics of the participants. Sudharsanan et al. (2020) also employed an RDD using nationally representative data on South African adults aged 30 years or older. The authors found that home-based screening reduced systolic blood pressure by 4.7 mmHg among women but not among men. Diastolic blood pressure was not affected by the intervention. When looking at socio- demographic characteristics, they found that systolic blood pressure decreased among adults aged 45 years or younger but not among older adults. They did not find any effect across education categories. The most recent study by Ciancio et al. (2021) estimated the effect of home-based screening on systolic and diastolic blood pressure levels, self-reported health behaviors, and self-reported physical and mental health. They used data on adults aged 45 years or older living in rural areas in three of the 28 districts in Malawi. In contrast to the other two studies, survey staff used a higher threshold to determine whether a participant had hypertension (160/110 mmHg in Ciancio et al. vs. 140/90 mmHg in Chen et al. and Sudharsanan et al.) and did not communicate any information on blood pressure control or hypertension but simply informed the participant about the measurement result and provided a referral slip. Their RDD analysis shows that home-based screening reduced both systolic and diastolic blood pressure, and increased hypertension diagnosis and the probability of having a controlled blood pressure. Hypertension treatment, health behavior (diet, physical activity), and knowledge on hypertension did not change through the intervention.

For increasing the share of individuals with hypertension who have a controlled blood pressure, it is important to consider the preceding two stages of the cascades of care, “awareness” and “treatment”. It is the loss of individuals at these two stages that governments urgently need to address and where they should put their focus on. Only the study by Ciancio et al. (2021) provide evidence on these two intermediary steps toward achieving hypertension control.

3.3 Data and outcome construction

Data

I used data from all six waves of the Centre for Cardiometabolic Risk Reduction in South Asia (CARRS) cohort.[109] The longitudinal survey was conducted between 2010 and 2018 (wave 1: October 2010 to November 2012; wave 2: November 2011 to March 2013; wave 3: March 2013 to April 2014; wave 4: February 2014 to June 2014; wave 5: January 2016 to February 2017; wave 6: January 2017 to April 2018) in Chennai and Delhi, two of the largest cities in India with a population of 4.6 million and 16.8 million, respectively.[110]

The survey employed a multi-stage cluster random sampling design yielding a sample representative of the population aged 20 years or older. Twenty municipal wards, the primary sampling unit, were randomly selected from Delhi and Chennai each. As a second step, five census enumeration blocks were randomly selected from each of the wards and a household listing was conducted. In each block, 20 households were randomly selected and, as the final step, one male and one female household member aged 20 years or older were randomly selected from each household.[109]

Blood pressure was measured in waves 1, 3, and 5, and information on previous hypertension diagnosis and current treatment were collected in all waves. For the analysis, I linked data from two consecutive waves treating the wave with blood pressure measurement as the baseline and the subsequent wave as follow-up providing information on self-reported hypertension diagnosis or treatment as outcomes. The data, thus, included three survey pairs. For the analysis, I pooled data from all three survey pairs. The inclusion criteria were: (i) an individual was 30 years or older at the baseline, which mirrors the age range targeted by the Indian

government's NPCDCS,[88] and (ii) no self-reported previous hypertension diagnosis or current treatment, respectively, at the baseline. Furthermore, I excluded all individuals that had no blood pressure measurement result or lacked information on self-reported hypertension diagnosis/treatment.

Blood pressure measurement

The CARRS study measured blood pressure as part of routine data collection in wave 1 (2010-2012), wave 3 (2013-2014), and wave 5 (2016-2017). Trained field staff recorded at least two blood pressure measurements toward the end of the interview using an Automated Omron HEM-7080 or HEM-708016 device.[111,112] Participants had to rest for five minutes before the first measurement was taken. A second measurement was taken at least 30 seconds after the first measurement. If the difference between the systolic blood pressure was more than 10 mmHg or in the diastolic blood pressure was more than 6 mmHg, a third measurement was taken.

The survey staff decided whether to refer an individual for formal diagnosis and treatment initiation based on the average of the last two measurements. If the average systolic blood pressure was ≥ 140 mmHg or the average diastolic blood pressure was ≥ 90 mmHg, the field staff informed the individual that they may have hypertension, provided basic information on the importance of hypertension control, and instructed them to visit a healthcare facility for a formal check-up. The field staff's activities are therefore comparable to a community-based screening intervention, where screeners visit people's homes, measure their blood pressure, and refer those with high blood pressure for formal care.

Outcomes

I investigated two outcomes, which both were measured at the follow-up. The first outcome is whether an individual was diagnosed with hypertension in the past 12 months. Table S7 displays the exact wording of the survey question used for this indicator in each wave. Only individuals that did not report a hypertension diagnosis in any of the earlier waves were included in the sample.

The second outcome is "current treatment", which consists of currently "taking any Allopathic drugs (English / modern)" for high blood pressure (Table S7). This information was only collected if an individual responded "yes" to the preceding question on hypertension diagnosis. Thus, this indicator should be interpreted as "among those who indicate that they were diagnosed in the past 12 months, who reported to currently take hypertension drugs?". The sample for the treatment outcome included all individuals irrespective of a hypertension diagnosis in any of the previous waves but excluded those that reported taking hypertension treatment at the baseline.

3.4 Methodology: Regression Discontinuity Design

The methodology of the RDD is explained in Section 2.4.1. Section 3.4 describes how the RDD was employed in the home-based screening study.

The running variable

The traditional RDD relies on one running variable and one threshold. However, in this study, individuals were referred if either their systolic *or* diastolic blood pressure was high. For this

reason, I standardized and combined the two measurements into one running variable resulting in one threshold.[75,93] First, I standardized each value by subtracting the threshold value (140 for systolic and 90 for diastolic blood pressure) from an individual's average measurement result and then dividing it by the sample's standard deviation. This resulted in an individual's standardized distance from the threshold for the systolic and diastolic blood pressure measurement, respectively. In a second step, I chose the larger distance to define where an individual was located relative to the threshold. In summary, I applied the following formula:

$$BPS = max\left[\left(\frac{sBP - 140}{sd(sBP)}; \frac{dBP - 90}{sd(dBP)}\right)\right] \quad (4)$$

with BPS = standardized blood pressure as the running variable, sBP = systolic blood pressure, dBP = diastolic blood pressure, and sd = standard deviation.

For example, in the analytical sample for the outcome "hypertension diagnosis", the standard deviation of the systolic blood pressure was 17.9 and of the diastolic blood pressure 11.2, which can be inserted into equation (4):

$$BPS = max\left[\left(\frac{sBP - 140}{17.9}; \frac{dBP - 90}{11.2}\right)\right] \quad (5)$$

For an individual with a blood pressure reading of 160/95 mmHg, equation (4) would translate into

$$BPS = max\left[\left(\frac{160-140}{17.9}, \frac{95-90}{11.2}\right)\right] = max[(1.1; 0.4)] = 1.1$$

If BPS < 0, the individual was below the threshold and did not receive the intervention. If BPS ≥ 0, the individual was above the threshold and, thus, received the intervention i.e. health information and the referral for hypertension care. With the combination of two thresholds and the standardization of the running variable, I took into account two crucial aspects: First, individuals who have, for example, high systolic but low diastolic blood pressure received the intervention. By using the larger of the standardized values, I accommodated this decision rule into the RDD analysis. Second, the characteristics of individuals further away from the threshold likely differed from those close to the threshold. I assumed this to also be the case for individuals who have, for example, a moderately high (or even low) diastolic blood pressure but considerably high systolic blood pressure. Again, by using the larger standardized value, these individuals were placed further away from the threshold as their characteristics (for example lifestyle or health seeking behavior) were more likely to correspond to someone with high blood pressure than low blood pressure. As the calculation of the running variable depends on the distribution of the underlying data, a separate running variable was generated for each model estimation (diagnosis outcome, treatment outcome, and for each of the sex, education, age, and previous cardiometabolic disease diagnosis subpopulations).

Equation (1)

In the home-based screening study in equation (1), Y_i is the probability of obtaining a formal hypertension diagnosis or treatment for individual *i*, X_i is the standardized blood pressure (BPS, the running variable), and D_i is a binary indicator that takes the value 1 if an individual had a standardized blood pressure of zero or higher. β_2 is the causal effect of the home-based

screening on hypertension diagnosis or treatment for individuals at the threshold, i.e. those with a standardized blood pressure of zero. Furthermore, I controlled for survey wave by adding a dummy for two of the three survey pairs and clustered standard errors at the individual-level.

Assumption 1: Discontinuous change in the probability of receiving the intervention at the threshold

The running variable X_i is the standardized blood pressure. To test whether Assumption 1 is likely to be fulfilled, I would need data on implementation fidelity. Unfortunately, information on whether study staff provided referrals to those (and only to those) with an average systolic blood pressure of 140 mmHg or higher or an average diastolic blood pressure of 90 mmHg or higher, is not available. However, based on the survey implementing agency's accounts, staff were instructed to strictly adhere to these guidelines. I, thus, assume that there was a sharp change in the probability of receiving a referral at the threshold. This discontinuity might not have been perfect but sufficient to consider Assumption 1 to be fulfilled.

Assumption 2: Continuity of the outcome at the threshold in the absence of the intervention

For this assumption to be fulfilled, no other interventions that would affect the outcome variables must be assigned based on an individual's blood pressure. The survey staff did not provide any other services or interventions based on the blood pressure measurement result. I, thus, assume that Assumption 2 is fulfilled.

Assumption 3: No systematic sorting around threshold

I assessed potential sorting around the threshold by plotting the frequency of blood pressure measurement results. Figure S4 shows no clustering of systolic or diastolic blood pressure

measurement results below nor above the threshold and, thus, I assume Assumption 3 to be fulfilled.

Heterogeneity analysis

Previous studies suggest that home-based screening can have a positive effect on health but that not everyone might benefit equally.[90–92] After having obtained information on hypertension, individuals need to visit a health care facility for formal diagnosis and treatment initiation. Then, they need to regularly take the medication to achieve blood pressure control. Previous studies show that certain population groups are more likely to act upon new health information than others.[98] To detect these differences, I estimated the RDD model for several subgroups of the population. First, I estimated the effect among the entire survey participant population and males and females separately to discover potential differences in health seeking behavior between genders.[98,113] Furthermore, I hypothesize that individuals with higher education are more likely to respond positively to the health information received.[114,115] I generated the following categories of educational attainment: Up to primary school completed, secondary school completed, and high school completed or higher education. To capture effect heterogeneities by age group, I split the sample into individuals aged 20-39 years and 40 years or older, based on the WHO-PEN guideline recommendation.[92,98,116] Another characteristic that might influence how an individual responds to health information might be previous diagnoses of other cardiometabolic diseases because this can indicate an already existing linkage to care.[117] Thus, I also estimated models disaggregated by diagnoses of other cardiometabolic diseases, specifically diabetes, stroke, or heart attack. Given that access to care and cultural specifics might influence how people seek care, I estimated the effect of home-based screening on hypertension diagnosis and treatment separately for each of the two cities, Chennai and Delhi.

3.5 Results

3.5.1 Sample description

Pooling observations from all three survey pairs yielded a dataset of 27,554 adults (100%) aged 30 years or older at the baseline (Figure 6). I excluded 6,238 individuals (23%) that did not participate in the follow-up survey and 990 (4%) because they did not have a valid blood pressure reading. For the hypertension diagnosis outcome, 615 (2%) observations were excluded because they did not have information on hypertension diagnosis at the baseline or follow-up. This resulted in 19,711 (72%) observations with the information required for the analysis of the diagnosis outcome. For this analysis, I excluded the 4,138 individuals who reported a previous hypertension diagnosis at the baseline or any earlier wave, resulting in a sample of 15,573 individuals. For the hypertension treatment outcome, also 615 (2%) did not have information on hypertension treatment at the baseline or follow up leaving 19,711 individuals (72%) with all the information required for the analysis of the treatment outcome. For this analysis, I excluded the 1,195 individuals who reported being on medication at the baseline resulting in a sample of 17,796 adults.

Table 5 displays the sample characteristics for the total population as well as the male and female subpopulations. The "overall" sample consists of all observations that were included in the study. The "analytical" sample includes only those observations that were within the MSE optimal bandwidth of the respective RDD model estimation. For both outcomes, characteristics were comparable across samples, for the total population, females, and males, and when comparing the overall and analytical samples. One notable difference was that the share of women aged 40 years or older was higher in the analytical than in the overall samples.

Figure 6: Number of observations included in analysis

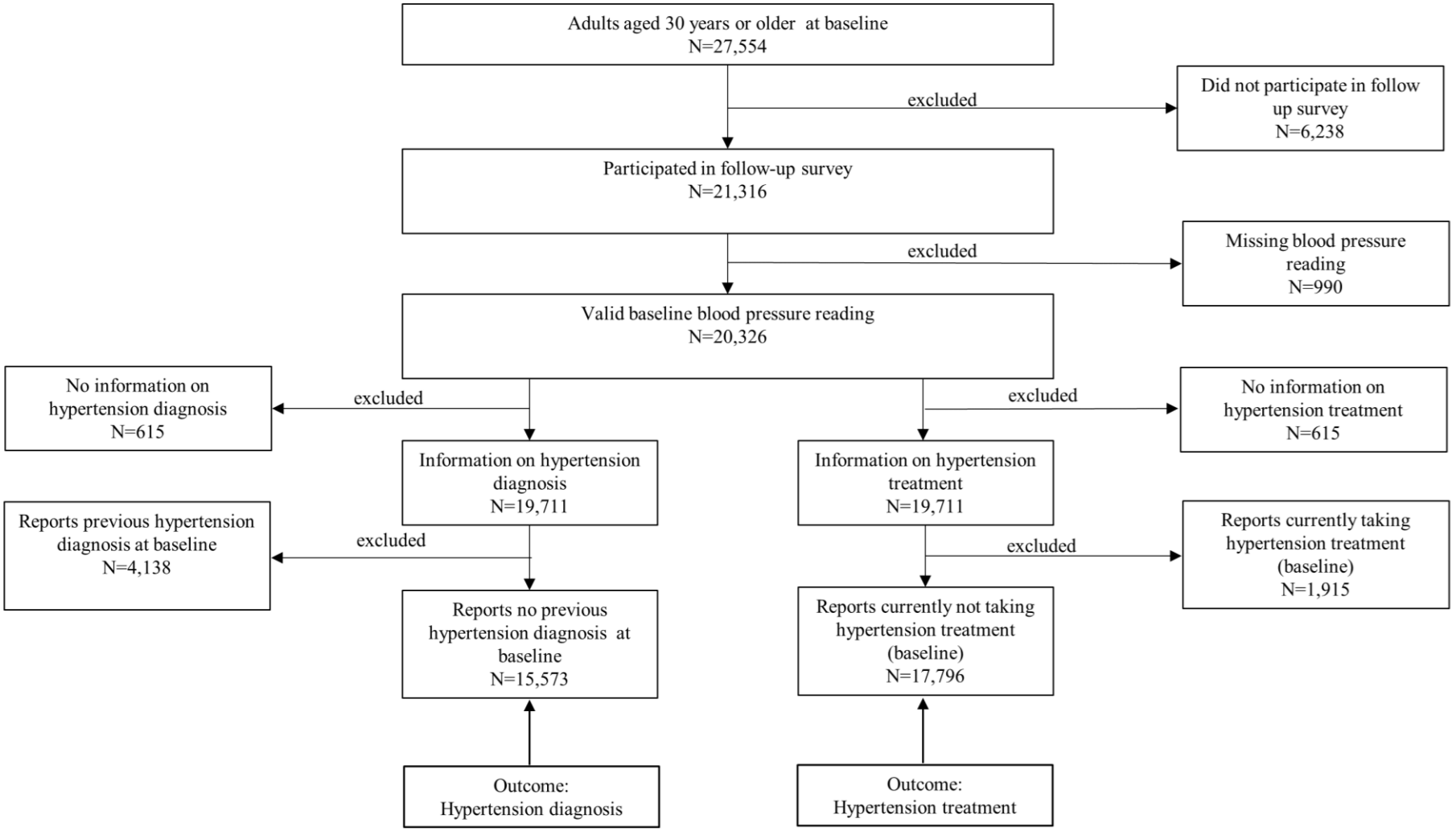


Table 5: Characteristics of the overall and analytic samples for adults ages 30 and older

	Hypertension diagnosis					
	Total		Females		Males	
Characteristic	Overall	Analytical	Overall	Analytical	Overall	Analytical
Number	15,573	7,977	8,122	3,347	7,451	4,312
Mean age, years (SD)	46 (11)	46 (11)	44 (10)	46 (10)	47 (12)	47 (11)
Age groups						
< 40 years (%)	33.9	29.9	37.1	29.0	30.4	29.8
≥ 40 years (%)	66.1	70.1	62.9	71.0	69.6	70.2
Religion						
Hindu (%)	80.3	79.6	81.0	80.3	79.6	79.2
Muslim (%)	10.2	10.9	9.6	10.3	11.0	11.3
Other (%)	9.4	9.6	9.4	9.4	9.4	9.5
Education categories						
Primary (%)	17.6	16.9	22.7	23.7	12.1	11.2
Secondary (%)	34.2	33.6	36.2	37.2	31.9	31.0
High school + (%)	48.2	49.5	41.0	39.1	56.0	57.9
Diabetes (%)	12.6	14.1	12.3	15.4	12.9	13.6
Heart attack (%)	2.1	2.0	1.1	1.1	3.1	2.7
Stroke (%)	0.9	0.8	0.4	0.5	1.4	1.2

	Hypertension treatment					
	Total		Females		Males	
Characteristic	Overall	Analytical	Overall	Analytical	Overall	Analytical
Number	17,796	8,456	9,408	4,266	8,388	5,072
Mean age, years (SD)	46 (11)	47 (11)	45 (11)	47 (11)	48 (12)	47 (12)
Age groups						
< 40 years (%)	31.3	27.1	34.0	26.4	28.4	28.2
≥ 40 years (%)	68.7	72.9	66.0	73.6	71.6	71.8
Religion						
Hindu (%)	80.2	79.6	80.5	79.5	79.9	79.6
Muslim (%)	10.3	10.7	9.9	10.5	10.6	10.8
Other (%)	9.5	9.7	9.6	10.0	9.5	9.6
Education categories						
Primary (%)	18.1	17.4	23.7	24.5	11.7	10.9
Secondary (%)	33.5	33.0	35.2	35.5	31.5	30.6
High school + (%)	48.4	49.6	41.0	40.0	56.7	58.5
Diabetes (%)	14.7	16.5	14.6	17.7	14.8	15.4
Heart attack (%)	2.7	2.5	1.7	1.7	3.8	3.3
Stroke (%)	1.4	1.3	0.9	1.0	1.9	1.6

Notes: The overall sample consists of all individuals meeting the eligibility criteria. The analytical sample consists of those individuals with a standardized blood pressure within the mean squared error optimal bandwidth of the main analysis.

Abbreviation: SD = standard deviation

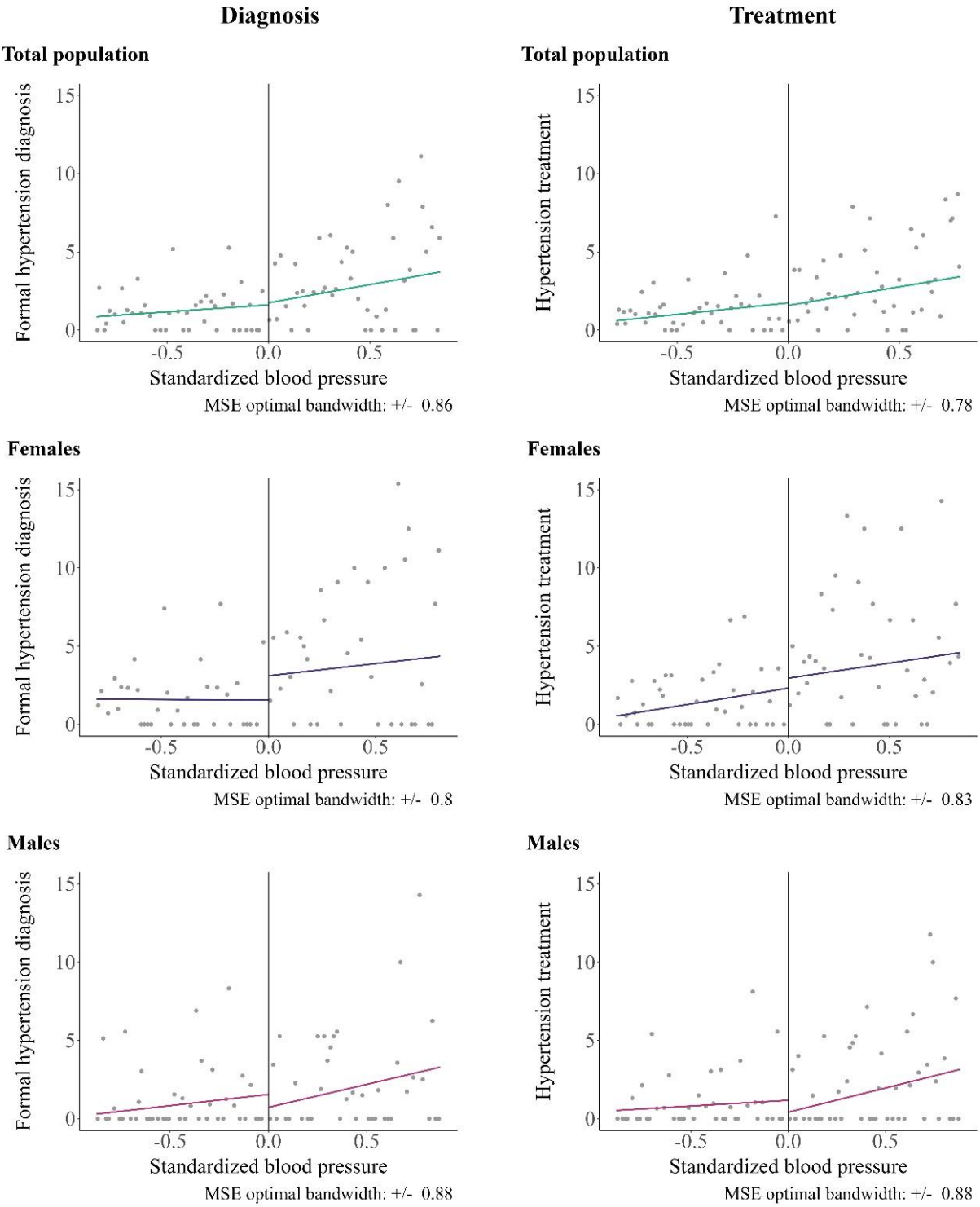
3.5.2 Regression Discontinuity Design results

I first plotted the standardized blood pressure measurement result against the probability of receiving a formal hypertension diagnosis for observations within the MSE optimal bandwidth. Then, I fitted the local linear trend to visually assess whether there might have been an effect of the intervention (Figure 7). The grey dots in the left panels of Figure 7 show that the probability of having received a hypertension diagnosis at the follow-up is low across the standardized blood pressure values within the bandwidth in all three samples (total population, females, males). Looking at the jump in the linear trends at the threshold, the figure suggests no effect of the home-based screening initiative on formal hypertension diagnosis in the total population, a small positive effect among females, and a small negative effect among males.

The results of the formal RDD estimation confirm the visual results: The point estimate in the total population is close to zero (0.1pp, 95% CI -1.4 - 1.7). There was a small positive but not statistically significant effect of the intervention on diagnosis among females (1.55pp, 95% CI -1.7 - 4.4) and a small negative non-significant effect among males (-0.8pp, 95% CI -2.5 - 0.8) (Table 6).

Similarly, I plotted the standardized blood pressure measurement against the probability of taking treatment for observations within the MSE optimal bandwidth (Figure 7, right panel). The visual pattern for the effect estimate of home-based screening on hypertension treatment was similar to, albeit smaller in magnitude than, the diagnosis results. In the total population, home-based screening did not seem to have an effect on hypertension treatment. It might have had a small positive effect among females and a small negative effect among males. The point estimates resulting from the RDD analysis confirmed this.

Figure 7: Hypertension diagnosis (left panel) and hypertension treatment (right panel) among adults aged 30 and older



Note: These plots only show observations within each mean squared error optimal bandwidth. The vertical line indicates the threshold set at a standardized blood pressure of zero. The colored lines represent the linear trends fitted separately for individuals with a standardized blood pressure below zero and those with a standardized blood pressure of zero or higher.

Table 6: Effect of home-based screening on hypertension diagnosis and treatment

	Total	Females	Males
Panel A: Diagnosis			
Estimation results			
Coefficient	0.12	1.55	-0.82
p-value	0.82	0.40	0.32
95% CI	(-1.39 - 1.75)	(-1.73 - 4.36)	(-2.50 - 0.81)
Bandwidth details			
Bandwidth	0.86	0.80	0.88
N (within bandwidth)	7,977	3,155	4,430
Panel B: Treatment			
Estimation results			
Coefficient	-0.16	0.64	-0.76
p-value	0.49	0.84	0.37
95% CI	(-2.18 - 1.03)	(-3.15 - 2.56)	(-2.28 - 0.86)
Bandwidth details			
Bandwidth	0.78	0.83	0.88
N (within bandwidth)	8,566	4,216	4,884

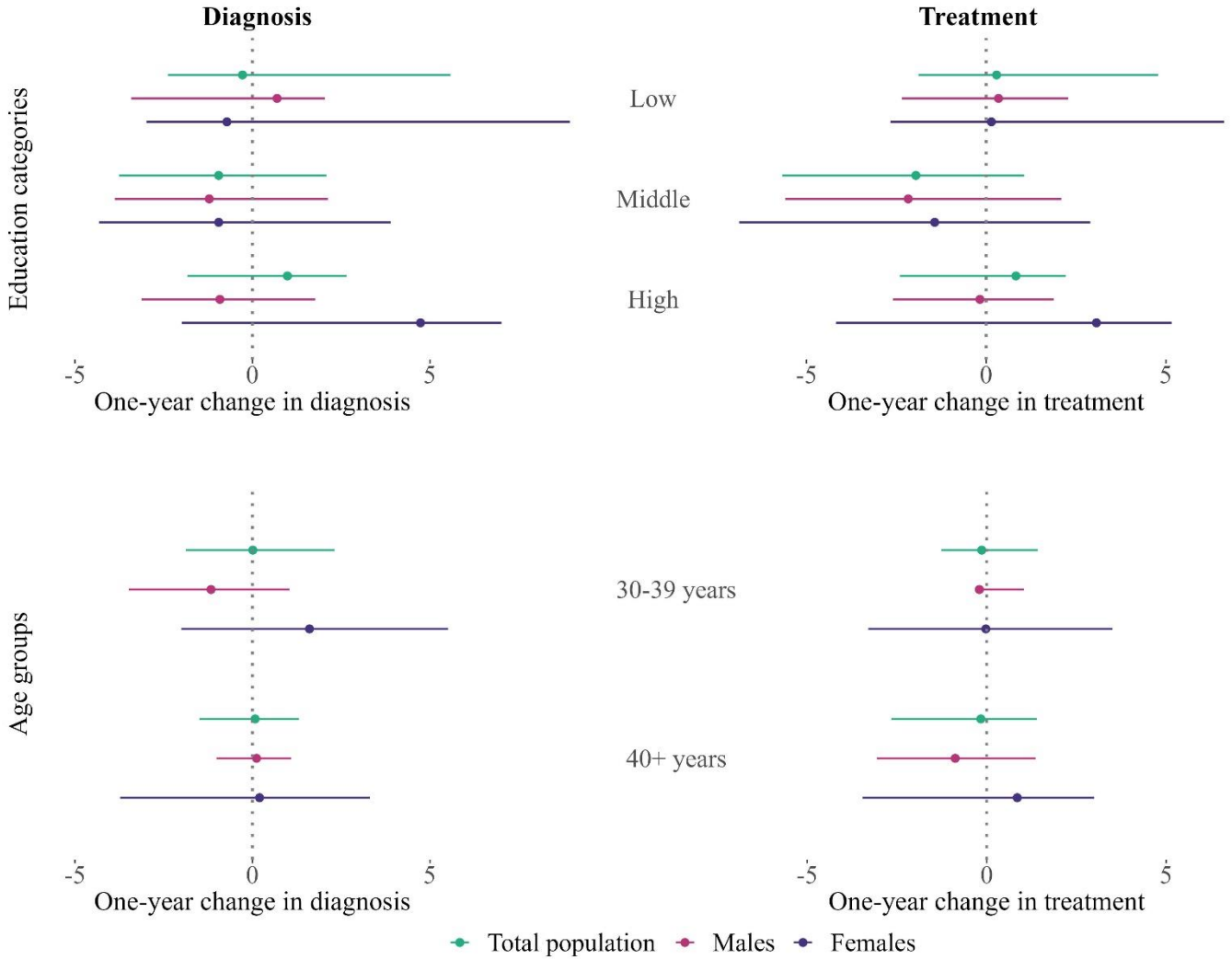
Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.
Abbreviation: CI = confidence interval

Effect sizes in the total population (-0.2pp, 95% CI -2.2 - 1.0), among females (0.6pp, 95% CI -3.2 - 2.6), and males (-0.8pp, 95% CI -2.3 - 0.9) were marginal and not statistically significant (Table 6).

In the next step, I analyzed whether there was heterogeneity in these effects across education and age and find that home-based screening did not affect hypertension diagnosis for the total

population, males, and females across education categories and age groups (Figure 8, Tables S8 and S9). Among women with high education, the point estimate (4.7pp, 95% CI -2.0 - 7.0) was considerably larger in magnitude than in the other education categories. This effect estimate is statistically insignificant with relatively wide confidence intervals. Similarly, the effect on the second outcome, hypertension treatment, did not vary across education categories or age groups in the total population, among males, or females (Figure 8, Tables S8 and S9). Again, a larger but insignificant point estimate could be observed among women with high education (3.07pp, 95% CI -4.17 - 5.16). A previous diagnosis of diabetes, heart attack, or stroke also did not show effect heterogeneities (Table 7). The point estimates among individuals without a previous cardiometabolic disease diagnosis were small in magnitude and not statistically significant. Among those with a previous diagnosis, point estimates across all three groups (total population, females, males) were negative (between -2 and -3pp) with relatively large confidence intervals, covering approximately +/- 6pp. In the final heterogeneity analysis, I divided the sample into individuals living in Chennai and Delhi. Across the total population, males, females in both cities and for both outcomes, the point estimates were close to zero and not statistically significant (Table 8). While the estimates were in the positive direction in Chennai, they were all negative in Delhi.

Figure 8: Regression Discontinuity Design results by education categories and age groups



Note: The figure displays the effect estimates and 95% confidence intervals of home-based hypertension screening on formal diagnosis (left panels) and treatment (right panels) by education category (top panels) and age group (bottom panels). Education categories are low education (up to primary school completed), middle education (secondary school completed), and high education (high school completed or higher). The model included linear local trends and triangular kernel weights, and estimated the effect within the mean squared error optimal bandwidth. The lower confidence interval of the treatment outcome of men aged 30-39 years was tiny and thus is not visible.

Table 7: Effect of home-based screening on hypertension diagnosis and treatment by previous diabetes, heart attack, or stroke diagnosis

	Diagnosis		Treatment	
	Other diagnosis	No other diagnosis	Other diagnosis	No other diagnosis
Panel A: Total				
Estimation results				
Coefficient	-2.03	0.66	-2.80	0.31
p-value	0.23	0.20	0.15	0.78
95% CI	(-10.34 - 2.53)	(-0.51 - 2.44)	(-10.30 - 1.55)	(-2.08 - 1.57)
Bandwidth details				
Bandwidth	0.75	0.75	0.74	0.74
N (within bandwidth)	1,121	5,689	1,495	6,579
Panel B: Females				
Estimation results				
Coefficient	-2.08	0.61	-2.90	0.29
p-value	0.23	0.23	0.14	0.77
95% CI	(-10.54 - 2.51)	(-0.56 - 2.33)	(-10.25 - 1.49)	(-2.08 - 1.54)
Bandwidth details				
Bandwidth	0.75	0.82	0.73	0.74
N (within bandwidth)	1,111	6,169	1,476	6,363
Panel C: Males				
Estimation results				
Coefficient	-2.00	0.66	-2.83	0.31
p-value	0.23	0.19	0.14	0.79
95% CI	(-10.38 - 2.45)	(-0.50 - 2.46)	(-10.14 - 1.43)	(-2.08 - 1.58)
Bandwidth details				
Bandwidth	0.76	0.73	0.74	0.72
N (within bandwidth)	1,125	5,615	1,495	6,363

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.
Abbreviation: CI = confidence interval

Table 8: Effect of home-based screening on hypertension diagnosis and treatment by city

	Diagnosis		Treatment	
	Chennai	Delhi	Chennai	Delhi
Panel A: Total				
Estimation results				
Coefficient	1.35	-0.75	0.54	-0.85
p-value	0.35	0.37	0.95	0.21
95% CI	(-1.38 - 3.94)	(-2.72 - 1.00)	(-3.00 - 2.81)	(-3.37 - 0.74)
Bandwidth details				
Bandwidth	0.85	0.98	0.88	0.77
N (within bandwidth)	3,712	4,346	4,525	4,346
Panel B: Females				
Estimation results				
Coefficient	1.33	-0.77	0.52	-0.85
p-value	0.37	0.38	0.95	0.21
95% CI	(-1.45 - 3.88)	(2.70 - 1.02)	(-2.95 - 2.77)	(-3.37 - 0.75)
Bandwidth details				
Bandwidth	0.86	0.95	0.91	0.78
N (within bandwidth)	3,704	4,434	4,514	4,337
Panel C: Males				
Estimation results				
Coefficient	1.34	-0.78	0.54	-0.84
p-value	0.35	0.40	0.94	0.21
95% CI	(-1.40 - 3.93)	(-2.67 - 1.06)	(-3.00 - 2.79)	(-3.38 - 0.76)
Bandwidth details				
Bandwidth	0.84	0.93	0.87	0.77
N (within bandwidth)	3,762	4,360	4,392	4,317

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.
Abbreviation: CI = confidence interval

3.5.3 Sensitivity analyses

To test the robustness of the results, I conducted a series of checks. First, one requirement for the internal validity of the RDD is that the individuals did not deliberately sort around the threshold, which would introduce bias. This would be the case, for example, if survey staff systematically attributed a blood pressure measurement result of 140/90 mmHg to those just below the threshold so that they could refer them to the healthcare facility for hypertension care. I tested this by plotting the number of occurrences of the measured systolic and diastolic blood pressure results to identify potential heaping around the threshold. As Figure S4 shows, there was no clustering of observations right at, just above, or just below the threshold suggesting that the survey staff correctly recorded the blood pressure measurement results.

Second, the result might be sensitive to the size of the bandwidth. The MSE optimal bandwidth balances the trade-off between bias and variance. Increasing the bandwidth will yield more precise estimates but increase the bias. Reducing the bandwidth will increase the variance but reduce the bias. To test the sensitivity of my results to the bandwidth size, I varied the bandwidth by +/-0.2 of the MSE optimal bandwidth in steps of 0.05 (Tables S10 and S11). The point estimates and the width of the 95% confidence intervals only marginally changed across different bandwidths. Thus, it can be concluded that the results are robust to changes in the bandwidth.

Third, the recall period of 12 months for hypertension diagnosis in survey pairs 1 and 2 does not necessarily cover the entire time period between pair baseline and follow-up. In pair 1 28% and in pair 2 4% of participants were followed-up more than twelve months after the baseline. If individuals went for a check-up right after the baseline survey but were followed up more

than 12 months later, they would report not having been diagnosed with hypertension in the past 12 months although they did go for a formal check-up following the recommendation received based on the baseline blood pressure measurement. Thus, I restricted the sample to only those individuals that were followed up at most 12 months after the baseline survey. The results show that the point estimates change marginally and confidence intervals become wider and continue to overlap with zero (Table S12). Thus, the effect estimates of the diagnosis outcome do not seem to be the result of the restricted length of the recall period.

Fourth, to also account for the fact that the recall period might not cover the entire time span between the baseline and follow-up interviews and to investigate whether the results might have been driven by one of the three pairs, I conducted the analysis separately for each of the pairs. The effect estimates remained statistically insignificant for both outcomes and across all waves, which indicates that the results from the main analysis were not driven by one specific survey pair (Table S13).

Fifth, the functional form of the local trend fitted within the bandwidth might affect the results. In the main analysis, I included a local linear trend, as recommended by Calonico et al (2019).[77] As a robustness check, I estimated a local quadratic trend. The results, point estimates as well as inference, are comparable to those from the main analysis, which indicates that they are robust to changes in the functional form (Table S14).

3.6 Discussion

Hypertension places a large health burden on the Indian population. Previous evidence shows that the majority of people living with hypertension are not aware of their condition and thus do not receive appropriate treatment.[99,100] Even among those who know that they have hypertension, only a small fraction take medication. To address this issue, large-scale home-based hypertension screening programs could be a cost-effective way of improving an individual's progression through the cascades of care. Such a program could raise awareness about an individual's hypertension status and increase care uptake by providing health information. Furthermore, it could encourage individuals who have previously been diagnosed but are currently not in treatment to seek care. Additionally, such an intervention could target the most vulnerable population groups, such as the elderly, people with disabilities, those living in remote and hard-to-reach areas, or those working long hours.

Previous studies in other countries showed that home-based screening improved blood pressure levels among individuals living with hypertension only to a limited extent.[90–93] My study on India adds to these results. I do not find an increase in hypertension diagnosis nor treatment uptake induced by home-based screening among the total population, males or females independent of education, age, and previous diagnosis of cardiometabolic diseases.

There is a variety of potential reasons why the home-based screening intervention did not increase hypertension diagnosis and treatment. I categorized them into three groups: individual-level, health system level, and intervention design.

At the individual level, the health information and referral provided by the survey team need to induce a behavior change. The individual needs to act on the information received and visit a health care facility for a formal hypertension diagnosis, obtain a prescription, and then take the medication regularly. This requires that they understand the information and perceive hypertension to be a threat to their health. As hypertension is usually asymptomatic individuals often do not perceive it to be a disease that requires immediate and sustained action, both in terms of initiating and adhering to care.[94,95] A second barrier is related to direct and opportunity costs. In India, the majority of individuals seek hypertension care in private facilities, which requires them to pay for the services provided and the medication.[96] Furthermore, depending on the distance to the nearest facility, they might incur travel costs. Travel time and the time spent at the facility, which in public facilities is particularly long, result in a loss of income as the individual cannot work during this time.[97] If the individual is aware that hypertension is a chronic condition, they might decide to not even obtain a formal diagnosis as they expect to not be able to afford treatment over a longer time period. Another reason for not seeking treatment might be the fear of potential side effects or dependence on a drug or a preference for alternative treatments.[94,95,97]

At the health system level, expanding hypertension screening coverage is essential for increasing hypertension diagnosis. Despite the Indian government's NMAP framework mandate to opportunistically screen all adults aged 30 years or older, in reality hypertension screening might not always take place.[89] If hypertension is not perceived as a priority by healthcare workers and patients do not feel comfortable asking for a blood pressure measurement, individuals following the referral by the home-based screening team might not obtain hypertension care although they acted on the health information received.[95,97] It also often is the case that healthcare workers are overburdened and do not dispose of sufficient time

and material resources, such as space for consultation, to screen individuals for hypertension and adherence support.[95]

The design of the home-based screening intervention may also have contributed to the null findings in my study. The field team used non-standardized health messages that might have been conveyed differently by different field staff. These messages might not have been phrased in a way that adequately conveys the information to the participant. Health literacy has been shown to be positively associated with blood pressure control.[118,119] The health messages provided should be tailored to the health literacy level of each individual and range from easily accessible to more elaborate phrasing. Participant's knowledge on hypertension might also influence whether fear-framed messages, i.e. emphasizing the risks of uncontrolled hypertension, or gain-framed messages, i.e. emphasizing the benefits of hypertension control, are more effective.[120] Furthermore, the health information should address any concerns and questions the participants might have, such as the fear of side effects and dependency or aspects such as asymptomatic hypertension and the persistence of the disease.

The Indian government is increasingly investing in home-based screening to improve population health. However, the results of my study suggest that this strategy may not be cost-effective yet. Therefore, it is crucial to investigate how to design home-based screening so that it effectively links individuals living with hypertension to care. The next steps to allow potential positive effects of home-based screening to unfold could be to test and evaluate different kinds of culturally sensitive, personalized health information messages. Furthermore, the program could include regular follow-ups by the same person to motivate an individual to visit a healthcare facility for formal diagnosis and treatment initiation. As having one contact person

can positively influence adherence, having the same physician for formal diagnosis, initiation, and follow-up visits could further contribute.[121] Another option would be to involve trained healthcare staff authorized to issue formal hypertension diagnoses and distribute medication on the spot eliminating the need for individuals to visit a healthcare facility. The last two approaches (regular follow-up and trained healthcare staff involvement) would, however, increase the complexity and cost of the intervention and their cost-effectiveness would have to be evaluated.

This study has several limitations. First, I was not able to investigate heterogeneities in the effect of home-based screening on hypertension diagnosis and treatment for socio-demographic characteristics other than sex, education, and age due to a lack of available data. In the Indian context, caste, religion, income, and type of occupation can be determinants of health seeking behavior and access to health services. Marginalized groups may face discrimination in the health care system, which might discourage them from seeking care unless it is urgently required.[122] Second, as the data were collected in two mega cities in India, the results cannot be generalized to the entire Indian population. One reason is that rural and urban areas differ vastly in terms of access to and demand for health services. Another reason is that India is a culturally rich and diverse country. While Chennai and Delhi are in two different parts of India and thus do capture some of the cultural variation, the results should not be generalized to urban centers in other parts of India. Third, the RDD estimates the local average treatment effect, which is the effect for individuals with a standardized blood pressure right at the threshold (i.e. zero). Home-based screening might affect hypertension diagnosis and treatment differently at different blood pressure values. For example, an individual with severely high blood pressure is more likely to be symptomatic and might thus have a bigger motivation to obtain treatment than a person with only slightly elevated blood pressure and no

symptoms. Fourth, the result of the blood pressure reading at the health care facility might differ from the measurement result during the home-based screening. If the blood pressure level was normal at the facility, an individual would not have been diagnosed despite acting on the referral by the survey staff, resulting in an underestimation of the treatment effect. Fifth, I do not have any information on implementation fidelity. While one of the robustness checks (Figure S4) indicated that interviewers did not manipulate the measurement results to influence whether participants received the intervention or not, it was not possible to verify whether eligible participants received health information and referrals from the survey staff. Thus, the estimates should be interpreted as an intention-to-treat effect.[92] Furthermore, I have no information on how exactly the health messages were conveyed, which might have influenced whether a participant sought follow-up care or not.

To conclude, this study contributes to the understanding of whether home-based screening can increase linkage to care. Although I do not find an effect in any of the studied population groups, it will be worthwhile to further explore potential channels and to redesign and re-evaluate existing home-based screening initiatives.

4. Conclusion

In the preceding chapters, I illustrated how quasi-experimental methods can be applied in the evaluation of population disease prevention programs if the intervention could not or was not randomly allocated. In the first study, I showed that the discontinuation of the BCG vaccine did not affect survival into adulthood. This indicates that the BCG vaccine did not have non-specific effects on survival in the Swedish population up to age 30. The second study showed that a home-based hypertension screening intervention in Delhi and Chennai did not increase

awareness about formal hypertension diagnosis or drug treatment initiation/adherence. The null effects in the two studies were observed across all populations and subpopulations.

The results of both studies were based on large sample sizes. Even in the subgroup analyses a large number of observations was included within the bandwidths, which resulted in narrow confidence intervals. Nevertheless, I did not detect any meaningful effects. Such precise effect estimates could probably not have been generated with an RCT. Data collection represents a substantial cost in RCTs. Thus, financial constraints might limit the number of observations included in each of the subgroups. This is even more relevant if the objective is to observe a "real life setting", where the study design does not aim to optimize the implementation of the intervention and compliance by participants, which can result in smaller true effect sizes.

The implementation of disease prevention programs commonly has two characteristics that lend themselves to quasi-experimental designs, specifically the RDD, RKD, and DiD. First, national-level policies are often implemented at a specific point in time. In the first study, this was the discontinuation of the BCG vaccine. Other examples include laws that mandate vaccinations at certain ages or the implementation of new prevention measures such as tobacco control laws or access to free condoms.[48,123,124] This clear and abrupt change in a policy can be exploited and the RDD, RKD, and DiD applied, as was shown in the BCG study. For example, could be evaluated how an increase in the tobacco tax affected a population's mortality or whether access to free condoms reduced sexually transmitted diseases. Second, the decision of whether an individual receives a preventive measure or not is often based on an arbitrary, pre-specified rule. In the home-based screening study, the decision whether to refer an individual to a health care facility was based on blood pressure. In medical practice, there is a multitude

of decision rules that are applied by healthcare workers on a daily basis. Common examples are the prescription of drugs, such as statins based on an individual's cardiovascular disease risk or diabetes medication based on the blood glucose level. The implementation of these decision rules provides the threshold needed in an RDD. For example, it can be evaluated in a real lifes scenario whether statins prevent heart attacks.

With quasi-experimental methods, it can be straightforward and inexpensive to estimate the impact of policies at the population level. The results would show whether a policy had the intended effect and raise new questions, for example, "why did home-based screening not work?". The answers to these new questions then need to be approached with primary research such as RCTs. Thus, quasi-experimental methods should not be seen as a substitute but rather a complement to RCTs. In the economic research community, quasi-experimental methods are widely used and increasingly applied to studies investigating health outcomes.[125–134] Among public health researchers, the application of these methods is becoming more popular but there is large unexploited potential.[13,14]

This potential will increase in the future for several reasons. First, over the past years, the benefits of "big data" have received increasing attention and it is expected that more governments and other institutions will implement systems to collect, store, and analyze these data.[135] Examples of big data in health care are routine patient data from hospitals or practices, health insurance claims, or data from wearable smart devices, such as smartwatches.[136] Second, while in the short to medium term Big Data will mainly become available from high-income countries, large population representative health surveys, such as the Demographic and Health Survey, continue to be conducted in low-income and middle-income countries.[137] By

repeatedly covering the same areas or even individuals, these surveys present a valuable data resource for the application of quasi-experimental methods. Third, with progresses in digitization and universal health coverage more data will become available covering an increasing share of the global population.

In conclusion, this thesis showed how quasi-experimental methods can be applied in the assessment of population prevention programs. This knowledge can be translated to other public health research questions benefitting from an increasing availability of large-scale datasets in the future.

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Appendix

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Table S 1: Multi-period Difference-in-Differences estimation results, reference year 1975

	Total	Females	Males
	Coefficient (95% CI) p-value	Coefficient (95% CI) p-value	Coefficient (95% CI) p-value
1950	0.04 (-0.19 - 0.27) 0.74	0.06 (-0.23 - 0.35) 0.68	0.00 (-0.35 - 0.36) 0.98
1951	-0.22 (-0.45 - 0.02) 0.07	-0.03 (-0.31 - 0.26) 0.86	-0.42 (-0.77 - -0.06) 0.02
1952	-0.02 (-0.25 - 0.21) 0.85	0.20 (-0.08 - 0.49) 0.16	-0.25 (-0.60 - 0.11) 0.17
1953	-0.17 (-0.40 - 0.06) 0.14	-0.05 (-0.33 - 0.24) 0.76	-0.29 (-0.65 - 0.06) 0.11
1954	-0.21 (-0.45 - 0.02) 0.07	0.09 (-0.20 - 0.38) 0.54	-0.50 (-0.85 - -0.14) 0.01
1955	-0.24 (-0.47 - -0.01) 0.04	-0.18 (-0.47 - 0.11) 0.22	-0.30 (-0.66 - 0.05) 0.09
1956	-0.05 (-0.28 - 0.18) 0.68	-0.07 (-0.36 - 0.22) 0.63	-0.02 (-0.37 - 0.34) 0.93
1957	-0.27 (-0.50 - -0.04) 0.02	-0.12 (-0.41 - 0.17) 0.41	-0.41 (-0.77 - -0.06) 0.02
1958	0.02 (-0.21 - 0.25) 0.89	0.16 (-0.13 - 0.45) 0.28	-0.12 (-0.47 - 0.24) 0.52
1959	-0.19 (-0.42 - 0.04) 0.11	-0.22 (-0.51 - 0.07) 0.14	-0.17 (-0.53 - 0.18) 0.35
1960	-0.28 (-0.51 - -0.05) 0.02	-0.17 (-0.46 - 0.12) 0.25	-0.40 (-0.76 - -0.04) 0.03
1961	-0.07 (-0.30 - 0.16) 0.57	-0.02 (-0.31 - 0.27) 0.88	-0.12 (-0.48 - 0.23) 0.50
1962	-0.06 (-0.29 - 0.17) 0.59	0.06 (-0.22 - 0.35) 0.67	-0.19 (-0.55 - 0.16) 0.29
1963	-0.16 (-0.38 - 0.07) 0.18	0.06 (-0.23 - 0.34) 0.70	-0.34 (-0.69 - 0.01) 0.06

	Total	Females	Males
	Coefficient (95% CI) *p-value*	Coefficient (95% CI) *p-value*	Coefficient (95% CI) *p-value*
1964	0.01 (-0.21 - 0.24) *0.92*	0.11 (-0.17 - 0.40) *0.43*	-0.11 (-0.46 - 0.24) *0.54*
1965	0.21 (-0.02 - 0.43) *0.07*	0.24 (-0.05 - 0.52) *0.10*	0.17 (-0.18 - 0.52) *0.34*
1966	-0.09 (-0.31 - 0.14) *0.46*	-0.08 (-0.37 - 0.20) *0.56*	-0.10 (-0.45 - 0.25) *0.58*
1967	-0.14 (-0.36 - 0.09) *0.24*	-0.11 (-0.39 - 0.17) *0.44*	-0.16 (-0.51 - 0.19) *0.37*
1968	-0.21 (-0.43 - 0.02) *0.07*	-0.07 (-0.36 - 0.21) *0.60*	-0.35 (-0.69 – 0.00) *0.05*
1969	0.01 (-0.22 - 0.24) *0.95*	0.11 (-0.18 - 0.39) *0.45*	-0.09 (-0.44 - 0.26) *0.61*
1970	-0.09 (-0.32 - 0.13) *0.42*	-0.18 (-0.46 - 0.11) *0.23*	-0.03 (-0.38 - 0.32) *0.86*
1971	0.01 (-0.21 - 0.24) *0.91*	0.02 (-0.27 - 0.30) *0.91*	0.01 (-0.34 - 0.36) *0.95*
1972	-0.12 (-0.34 - 0.11) *0.32*	0.02 (-0.27 - 0.31) *0.89*	-0.25 (-0.6 - 0.10) *0.17*
1973	-0.13 (-0.36 - 0.10) *0.29*	-0.08 (-0.36 - 0.21) *0.61*	-0.18 (-0.54 - 0.17) *0.31*
1974	-0.09 (-0.33 - 0.14) *0.42*	-0.16 (-0.45 - 0.13) *0.28*	-0.02 (-0.38 - 0.34) *0.91*
1975	*Ref.*	*Ref.*	*Ref.*
1976	-0.17 (-0.41 - 0.07) *0.17*	-0.05 (-0.34 - 0.25) *0.76*	-0.28 (-0.65 - 0.09) *0.13*
1977	-0.08 (-0.32 - 0.16) *0.53*	-0.12 (-0.42 - 0.18) *0.43*	-0.03 (-0.40 - 0.34) *0.86*
1978	-0.01 (-0.25 - 0.23) *0.92*	0.32 (0.01 - 0.62) *0.04*	-0.33 (-0.70 - 0.04) *0.08*
1979	0.00 (-0.24 - 0.24) *0.98*	-0.04 (-0.34 - 0.26) *0.80*	0.03 (-0.34 - 0.40) *0.86*

	Total	Females	Males
	Coefficient (95% CI) *p-value*	Coefficient (95% CI) *p-value*	Coefficient (95% CI) *p-value*
1980	-0.13 (-0.37 - 0.11) *0.30*	0.03 (-0.27 - 0.33) *0.83*	-0.29 (-0.66 - 0.08) *0.13*
1981	-0.10 (-0.34 - 0.14) *0.40*	-0.04 (-0.35 - 0.26) *0.77*	-0.15 (-0.52 - 0.22) *0.43*
1982	-0.19 (-0.43 - 0.06) *0.13*	-0.05 (-0.35 - 0.25) *0.76*	-0.32 (-0.69 - 0.06) *0.10*
1983	-0.25 (-0.49 - -0.01) *0.04*	-0.11 (-0.42 - 0.19) *0.47*	-0.38 (-0.76 - -0.01) *0.04*
1984	-0.09 (-0.33 - 0.15) *0.46*	0.02 (-0.28 - 0.32) *0.89*	-0.19 (-0.57 - 0.18) *0.31*
1985	-0.24 (-0.48 - 0.00) *0.05*	-0.13 (-0.43 - 0.17) *0.39*	-0.35 (-0.72 - 0.02) *0.07*
1986	-0.34 (-0.58 - -0.10) *0.00*	-0.12 (-0.42 - 0.18) *0.43*	-0.56 (-0.93 - -0.19) *0.00*
1987	-0.31 (-0.54 - -0.07) *0.01*	0.05 (-0.25 - 0.34) *0.75*	-0.65 (-1.01 - -0.28) *0.00*
1988	-0.27 (-0.50 - -0.04) *0.02*	-0.03 (-0.32 - 0.26) *0.85*	-0.50 (-0.86 - -0.14) *0.01*

Note: Coefficients are the difference in the probability of survival between cohorts born in the respective year in Sweden and Norway net the secular time trend and fixed countries differences. The reference group is the cohort born in 1975, the year of the Bacillus Calmette–Guérin vaccine discontinuation.
Abbreviations: CI = confidence interval

Table S 2: Regression Discontinuity Design estimation results, threshold year 1975

	Total	Females	Males
Estimation results			
Coefficient	0.06	0.09	0.02
p-value	0.59	0.51	0.73
95% CI	(-0.27 - 0.38)	(-0.21 - 0.42)	(-0.47 - 0.67)
Bandwidth details			
Bandwidth	4.03	4.79	3.37
N (within bandwidth)	933,831	453,278	372,066

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The table displays the local average treatment effect for the birth cohort of 1975 and confidence intervals resulting from robust bias-corrected standard errors.
Abbreviations: CI = confidence interval

Table S 3: Regression Kink Design estimation results, threshold year 1975

	Total	Females	Males
Estimation results			
Coefficient	0.03	-0.19	0.14
p-value	0.74	0.37	0.47
95% CI	(-0.35 - 0.49)	(-4.5 - 1.66)	(-1.06 - 2.29)
Bandwidth details			
Bandwidth	6.22	5.31	4.04
N (within bandwidth)	1,342,732	554,090	480,553

Note: The model estimation included a local quadratic trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). For the female subsample, the model included a local cubic trend as the local quadratic trend did not fit the data structure. The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The table displays the local average treatment effect for the birth cohort of 1975 and confidence intervals resulting from robust bias-corrected standard errors.
Abbreviations: CI = confidence interval

Table S 4: Pooled Difference-in-Differences estimation results, threshold year 1974

	Total	Females	Males
All observations			
Coefficient	-0.05	-0.02	-0.08
p-value	0.05	0.56	0.07
95% CI	(-0.11 - 0.00)	(-0.09 - 0.05)	(-0.16 - 0.01)
Within bandwidth			
Coefficient	0.01	0.05	0.06
p-value	0.85	0.46	0.51
95% CI	(-0.09 - 0.11)	(-0.07 - 0.17)	(-0.11 - 0.23)

Note: I pooled data from all pre-discontinuation and post-discontinuation years respectively. Regression models include year dummies. The mean squared error optimal bandwidth was 4 for the full population, 4 for the female population, and 3 for the male population. The reference year was 1974.

Table S 5: Regression Discontinuity Design estimation results with increasing bandwidth, threshold year 1976

	MSE + 1 year	MSE + 2 years	MSE + 3 years
Panel A: Total			
Estimation results			
Coefficient	0.02	0.04	0.04
p-value	0.66	0.73	0.96
95% CI	(-0.30 - 0.19)	(-0.23 - 0.16)	(-0.18 - 0.17)
Bandwidth details			
Bandwidth	4.95	5.95	6.95
N (within bandwidth)	916,411	1,124,960	1,327,858
Panel B: Females			
Estimation results			
Coefficient	-0.10	-0.05	-0.04
p-value	0.26	0.25	0.45
95% CI	(-0.84 - 0.23)	(-0.64 - 0.17)	(-0.46 - 0.21)
Bandwidth details			
Bandwidth	5.75	6.75	8.75
N (within bandwidth)			
Panel B: Males			
Estimation results			
Coefficient	0.04	0.05	0.04
p-value	0.79	0.80	0.70
95% CI	(-0.22 - 0.29)	(-0.20 - 0.26)	(-0.17 - 0.25)
Bandwidth details			
Bandwidth	7.09	8.09	9.09
N (within bandwidth)	785,759	892,220	1,005,496

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (MSE optimal bandwidth). The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The table displays the local average treatment effect for the birth cohort of 1976 and confidence intervals resulting from robust bias-corrected standard errors. I increased the MSE optimal bandwidth by one, two, and three years respectively as a robustness check.
Abbreviations: CI = confidence interval; MSE = mean squared error

Table S 6: Regression Kink Design estimation results with increasing bandwidth, threshold year 1976

	MSE + 1 year	MSE + 2 years	MSE + 3 years
Panel A: Total			
Estimation results			
Coefficient	-0.08	-0.06	-0.06
p-value	0.67	0.45	0.58
95% CI	(-0.69 - 0.45)	(-0.53 - 0.23)	(-0.36 - 0.02)
Bandwidth details			
Bandwidth	6.00	7.00	8.00
N (within bandwidth)	1,124,960	1,327,858	1,527,260
Panel B: Females			
Estimation results			
Coefficient	-0.02	0.02	0.02
p-value	0.41	0.41	0.80
95% CI	(-1.03 - 0.42)	(-0.69 - 0.28)	(-0.41 - 0.31)
Bandwidth details			
Bandwidth	5.76	6.76	7.76
N (within bandwidth)	546,416	645,040	741,501
Panel B: Males			
Estimation results			
Coefficient	-0.12	-0.14	-0.13
p-value	0.94	0.84	0.65
95% CI	(-0.39 - 0.16)	(-0.34 - 0.07)	(0.30 - 0.03)
Bandwidth details			
Bandwidth	5.30	6.30	7.30
N (within bandwidth)	578,544	682,818	785,759

Note: The model estimation included a local quadratic trend, triangular Kernel weights, and a data-driven bandwidth selection (MSE optimal bandwidth). The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The precise mean squared error optimal bandwidth in the total population was 4.9996, with a floor of 4. The table displays the local average treatment effect for the birth cohort of 1976 and confidence intervals resulting from robust bias-corrected standard errors. I increased the MSE optimal bandwidth by one, two, and three years respectively as a robustness check.
Abbreviations: CI = confidence interval; MSE = mean squared error

Table S 7: Survey Questions on hypertension diagnosis and treatment

Survey pair	Wave	Diagnosis	Treatment
Pair 1	wave 1: 2010-2012	Have you ever been told by a doctor that you have any of the following diseases? Hypertension (high blood pressure)	What treatment are you taking for it currently? Allopathic drugs (English/modern)
	wave 2: 2011-2013	In last one year, have you been told by a doctor that you have developed or suffered (or started medication for) any of the following diseases? Hypertension (high blood pressure)	Are you taking any Allopathic drugs (English/modern) for your blood pressure?
Pair 2	wave 3: 2013-2014	In last one year, have you been told by a doctor that you have developed or suffered (or started medication for) any of the following diseases? Hypertension (high blood pressure)	Are you taking any Allopathic drugs (English/modern) for your blood pressure?
	wave 4: 2014	In last one year, have you been told by a doctor that you have developed or suffered (or started medication for) any of the following diseases? Hypertension (high blood pressure)	Are you taking any Allopathic drugs (English/modern) for your blood pressure?
Pair 3	wave 5: 2016-2017	Have you EVER been told by a doctor that you have any of the following diseases? Hypertension (high blood pressure)	What treatment are you taking for it currently? Allopathic drugs (English/modern)
	wave 6: 2017-2018	Have you EVER been told by a doctor that you have any of the following diseases? Hypertension (high blood pressure)	What treatment is you taking for it currently? Allopathic drugs (English/modern)

Table S 8: Effect of home-based screening on hypertension diagnosis and treatment by education category

	Diagnosis			Treatment		
	Low	Middle	High	Low	Middle	High
Panel A: Total						
Estimation results						
Coefficient	-0.28	-0.95	0.99	0.29	-1.96	0.83
p-value	0.43	0.57	0.72	0.39	0.18	0.94
95% CI	(-2.38 - 5.58)	(-3.75 - 2.08)	(-1.83 - 2.66)	(-1.89 - 4.79)	(-5.67 - 1.06)	(-2.40 - 2.21)
Bandwidth details						
Bandwidth	0.72	0.77	0.72	0.67	0.67	0.69
N (within bandwidth)	1,158	2,441	3,107	1,295	2,396	3,583
Panel B: Females						
Estimation results						
Coefficient	-0.72	-0.95	4.74	0.15	-1.43	3.07
p-value	0.33	0.92	0.27	0.40	0.43	0.84
95% CI	(-2.98 - 8.94)	(-4.32 - 3.90)	(-1.99 - 7.02)	(-2.67 - 6.62)	(-6.87 - 2.90)	(-4.17 - 5.16)
Bandwidth details						
Bandwidth	0.69	1.11	0.79	0.71	0.91	0.84
N (within bandwidth)	699	1,692	1,209	909	1,604	1,641
Panel C: Males						
Estimation results						
Coefficient	0.70	-1.21	-0.92	0.34	-2.17	-0.17
p-value	0.62	0.57	0.59	0.98	0.37	0.75
95% CI	(-3.41 - 2.04)	(-3.88 - 2.12)	(-3.13 - 1.77)	(-2.35 - 2.28)	(-5.59 - 2.09)	(-2.60 - 1.88)
Bandwidth details						
Bandwidth	0.57	0.75	0.70	0.53	0.71	0.64
N (within bandwidth)	337	1,183	1,955	347	1,284	2,055

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of 0 and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level. Low education refers to education up to primary school completed, middle education to secondary school completed, and high education to high school completed or higher.

Abbreviation: CI = confidence interval

Table S 9: Effect of home-based screening on hypertension diagnosis and treatment by age group

	Diagnosis		Treatment	
	30-39 years	40+ years	30-39 years	40+ years
Panel A: Total				
Estimation results				
Coefficient	0.08	0.01	-0.14	-0.16
p-value	0.90	0.84	0.91	0.54
95% CI	(-1.49 - 1.31)	(-1.87 - 2.31)	(-1.26 - 1.43)	(-2.65 - 1.39)
Bandwidth details				
Bandwidth	0.60	0.85	0.66	0.83
N (within bandwidth)	1,444	5,668	1,752	6,640
Panel B: Females				
Estimation results				
Coefficient	0.20	1.61	-0.02	0.85
p-value	0.91	0.36	0.95	0.89
95% CI	(-3.72 - 3.31)	(-2.00 - 5.52)	(-3.30 - 3.51)	(-3.45 - 2.99)
Bandwidth details				
Bandwidth	0.69	0.81	0.69	0.98
N (within bandwidth)	676	2,405	730	3,700
Panel C: Males				
Estimation results				
Coefficient	0.12	-1.17	-0.20	-0.88
p-value	0.94	0.29	0.29	0.45
95% CI	(-1.01 - 1.09)	(-3.48 - 1.04)	(-0.31 - 1.04)	(-3.06 - 1.36)
Bandwidth details				
Bandwidth	0.57	0.94	0.61	0.85
N (within bandwidth)	810	3,373	901	3,543

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.
Abbreviation: CI = confidence interval

Table S 10: Effect of home-based screening on hypertension diagnosis with varying bandwidths

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Panel A: Total									
Estimation results									
Coefficient	0.12	0.13	0.17	0.16	0.12	0.09	0.09	0.09	0.10
p-value	0.70	0.79	0.87	0.87	0.82	0.79	0.81	0.84	0.86
95% CI	(-1.39-2.06)	(-1.45-1.91)	(-1.51-1.77)	(-1.47-1.73)	(-1.39-1.75)	(-1.33-1.75)	(-1.32-1.70)	(-1.33-1.63)	(-1.33-1.59)
Bandwidth details									
Bandwidth	0.66	0.71	0.76	0.81	0.86	0.91	0.96	1.01	1.06
N (within bandwidth)	5,915	6,398	7,132	7,611	7,977	8,386	8,786	9,217	9,528
Panel B: Females									
Estimation results									
Coefficient	1.42	1.41	1.45	1.51	1.55	1.50	1.41	1.32	1.30
p-value	0.34	0.33	0.37	0.39	0.40	0.35	0.29	0.25	0.25
95% CI	(-1.84-5.32)	(-1.72-5.07)	(-1.76-4.76	(-1.77-4.52)	(-1.73-4.36)	(-1.55-4.37)	(-1.32-4.47)	(-1.16-4.51)	(-1.13-4.43)
Bandwidth details									
Bandwidth	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
N (within bandwidth)	2,316	2,523	2,742	2,972	3,155	3,537	3,762	3,973	4,134
Panel C: Males									
Estimation results									
Coefficient	-0.86	-0.86	-0.84	-0.84	-0.82	-0.79	-0.74	-0.70	-0.67
p-value	0.47	0.42	0.37	0.35	0.32	0.28	0.24	0.22	0.20
95% CI	(-2.36-1.09)	(-2.43-1.01)	(-2.49-0.93)	(-2.49-0.87)	(-2.50-0.81)	(-2.52-0.74)	(-2.55-0.65)	(-2.56-0.59)	(-2.55-0.54)
Bandwidth details									
Bandwidth	0.68	0.73	0.78	0.83	0.88	0.93	0.98	1.03	1.08
N (within bandwidth)	3,421	3,672	3,836	4,211	4,430	4,611	4,769	4,936	5,133

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and CIs resulting from robust bias-corrected standard errors clustered at the individual-level. The bandwidth was varied by +/- 0.2 in intervals of 0.05, column (5) contains the results of the main analysis
Abbreviation: CI = confidence interval

Table S 11: Effect of home-based screening on hypertension treatment with varying bandwidths

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Panel A: Total									
Estimation results									
Coefficient	-0.37	-0.30	-0.24	-0.17	-0.16	-0.15	-0.14	-0.11	-0.09
p-value	0.61	0.53	0.48	0.44	0.49	0.53	0.55	0.55	0.56
95% CI	(-2.32-1.37)	(-2.35-1.20)	(-2.33-1.09)	(-2.30-1.01)	(-2.18-1.03)	(-2.06-1.06)	(-1.98-1.06)	(-1.93-1.03)	(-1.88-1.02)
Bandwidth details									
Bandwidth	0.58	0.63	0.68	0.73	0.78	0.83	0.88	0.93	0.98
N (within bandwidth)	6,212	6,695	7,223	7,745	8,566	9,075	9,530	9,985	10,451
Panel B: Females									
Estimation results									
Coefficient	0.20	0.38	0.52	0.61	0.64	0.66	0.72	0.76	0.81
p-value	0.85	0.76	0.74	0.76	0.84	0.91	0.93	0.96	1.00
95% CI	(-3.60-2.97)	(-3.65-2.67)	(-3.56-2.53)	(-3.40-2.49)	(-3.15-2.56)	(-2.94-2.62)	(-2.85-2.59)	(-2.72-2.59)	(-2.60-2.59)
Bandwidth details									
Bandwidth	0.63	0.68	0.73	0.78	0.83	0.88	0.93	0.98	1.03
N (within bandwidth)	3,008	3,409	3,677	3,929	4,216	4,417	4,631	4,877	5,129
Panel C: Males									
Estimation results									
Coefficient	-0.75	-0.73	-0.75	-0.76	-0.76	-0.76	-0.74	-0.74	-0.71
p-value	0.43	0.39	0.40	0.39	0.37	0.36	0.33	0.31	0.28
95% CI	(-2.47-1.04)	(-2.45-0.95)	(-2.37-0.94)	(-2.32-0.90)	(-2.28-0.86)	(-2.25-0.81)	(-2.23-0.75)	(-2.20-0.71)	(-2.21-0.64)
Bandwidth details									
Bandwidth	0.68	0.73	0.78	0.83	0.88	0.93	0.98	1.03	1.08
N (within bandwidth)	3,968	4,197	4,460	4,717	4,884	5,219	5,404	5,615	5,804

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The derivation of the optimal bandwidth can result in a decimal. In line with Cattaneo et al. (2019), I used the floor of the decimal. The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of 0 and confidence intervals resulting from robust bias-corrected standard errors. The bandwidth was varied by +/- 0.2 in intervals of 0.05, column (5) contains the results of the main analysis
Abbreviation: CI = confidence interval

Table S 12: Effect of home-based screening on hypertension diagnosis and treatment (restricted to follow-up observations in each pair surveyed at most 12 months after baseline)

	Total	Females	Males
Panel A: Diagnosis			
Estimation results			
Coefficient	-0.03	0.62	-0.72
p-value	0.92	0.41	0.34
95% CI	(-1.46 - 1.63)	(-1.79 - 4.37)	(-1.81 - 0.63)
Bandwidth details			
Bandwidth	1.00	1.01	0.66
N (within bandwidth)	7,283	3,359	2,645
Panel B: Treatment			
Estimation results			
Coefficient	-0.40	0.59	-0.72
p-value	0.31	0.82	0.34
95% CI	(-2.68 - 0.86)	(-3.63 - 2.89)	(-1.81 - 0.63)
Bandwidth details			
Bandwidth	0.96	0.95	0.66
N (within bandwidth)	8,346	3,968	2,645

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.
Abbreviation: CI = confidence interval

Table S 13: Effect of home-based screening on hypertension diagnosis and treatment by pair

	Total			Female			Male		
	Pair 1	Pair 2	Pair 3	Pair 1	Pair 2	Pair 3	Pair 1	Pair 2	Pair 3
Panel A: Diagnosis									
Estimation results									
Coefficient	1.67	-0.30	-1.39	2.91	0.10	1.01	0.46	-0.75	-3.18
p-value	0.09	0.55	0.65	0.09	0.83	0.96	0.56	0.63	0.21
95% CI	(-0.33-4.15)	(-2.64-1.41)	(-5.62-3.49)	(-0.52-7.91)	(-3.20-2.57)	(-8.03-8.42)	(-1.53-2.82)	(-3.43-2.06)	(-7.15-1.56)
Bandwidth details									
Bandwidth	0.76	0.79	0.66	0.80	0.74	0.68	0.90	0.74	0.78
N (within bandwidth)	2,562	2,445	1,658	1,248	1,041	813	1,685	1,250	1,108
Panel B: Treatment									
Estimation results									
Coefficient	1.66	-1.43	-1.13	2.83	-1.91	0.50	0.60	-0.84	-2.30
p-value	0.12	0.17	0.47	0.11	0.16	0.99	0.75	0.55	0.24
95% CI	(-0.45-4.00)	(-5.15-0.89)	(-4.76-2.18)	(-0.74-7.25)	(-8.55-1.40)	(-6.19-6.24)	(-1.87-2.62)	(-4.07-2.16)	(-6.03-1.48)
Bandwidth details									
Bandwidth	0.67	0.64	0.87	0.79	0.66	0.87	0.73	0.83	0.73
N (within bandwidth)	2,502	2,518	2,716	1,382	1,259	1,325	1,412	1,699	1,219

Note: The model estimation included a local linear trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.

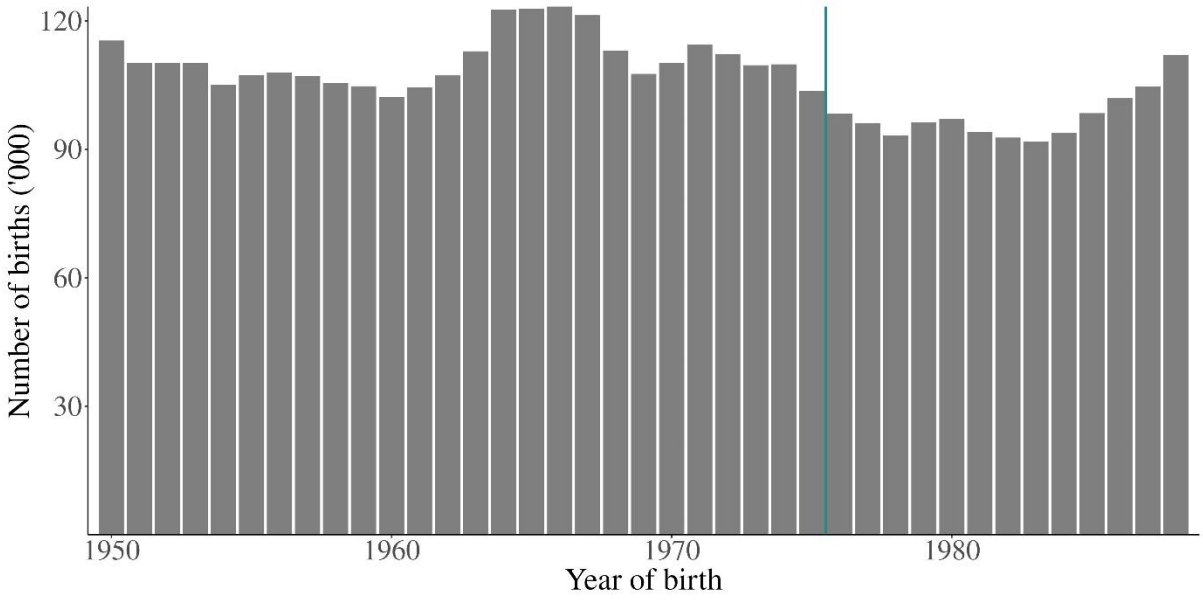
Abbreviation: CI = confidence interval

Table S 14: Effect of home-based screening on hypertension diagnosis and treatment with a local quadratic trend

	Total	Females	Males
Panel A: Diagnosis			
Estimation results			
Coefficient	0.20	1.55	-0.72
p-value	0.71	0.49	0.97
95% CI	(-1.47 - 2.17)	(-2.21 - 4.62)	(-1.77 - 1.83)
Bandwidth details			
Bandwidth	1.04	1.11	0.84
N (within bandwidth)	9,528	4,589	4,211
Panel B: Treatment			
Estimation results			
Coefficient	-0.46	0.62	-0.72
p-value	0.31	0.59	0.97
95% CI	(-2.92 - 0.94)	(-4.46 - 2.53)	(-1.77 - 1.83)
Bandwidth details			
Bandwidth	1.22	1.21	0.84
N (within bandwidth)	12,619	6,132	4,211

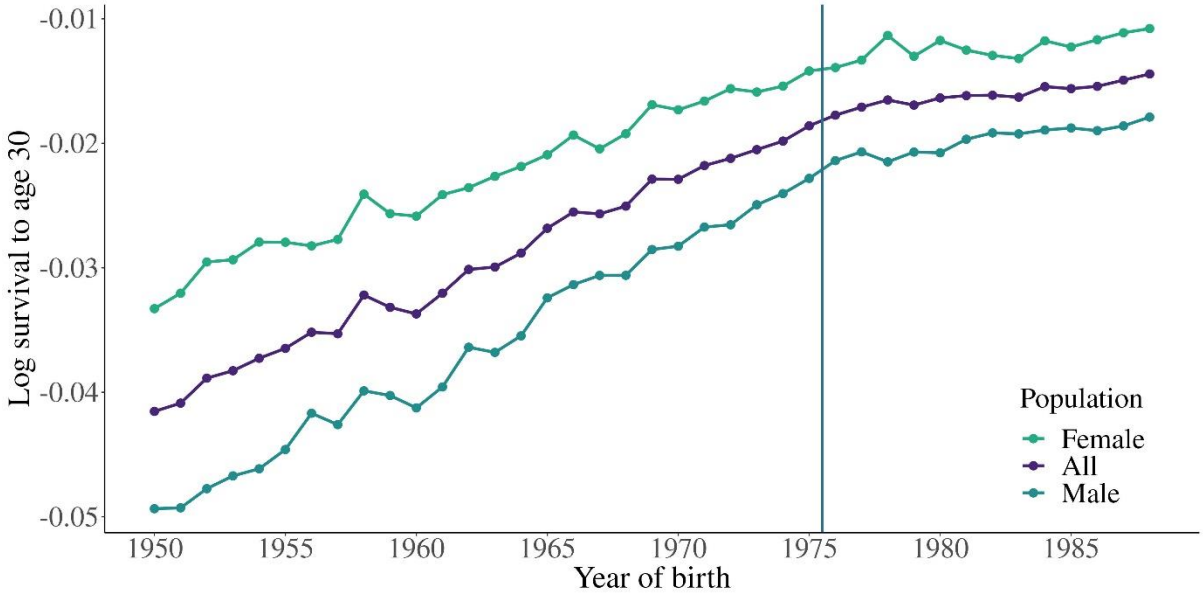
Note: The model estimation included a local quadratic trend, triangular Kernel weights, and a data-driven bandwidth selection (mean squared error optimal bandwidth). The table displays the local average treatment effect in percentage points for individuals with a standardized blood pressure of zero and confidence intervals resulting from robust bias-corrected standard errors clustered at the individual-level.
Abbreviation: CI = confidence interval

Figure S 1: Number of births (in thousands), years 1950 - 1988



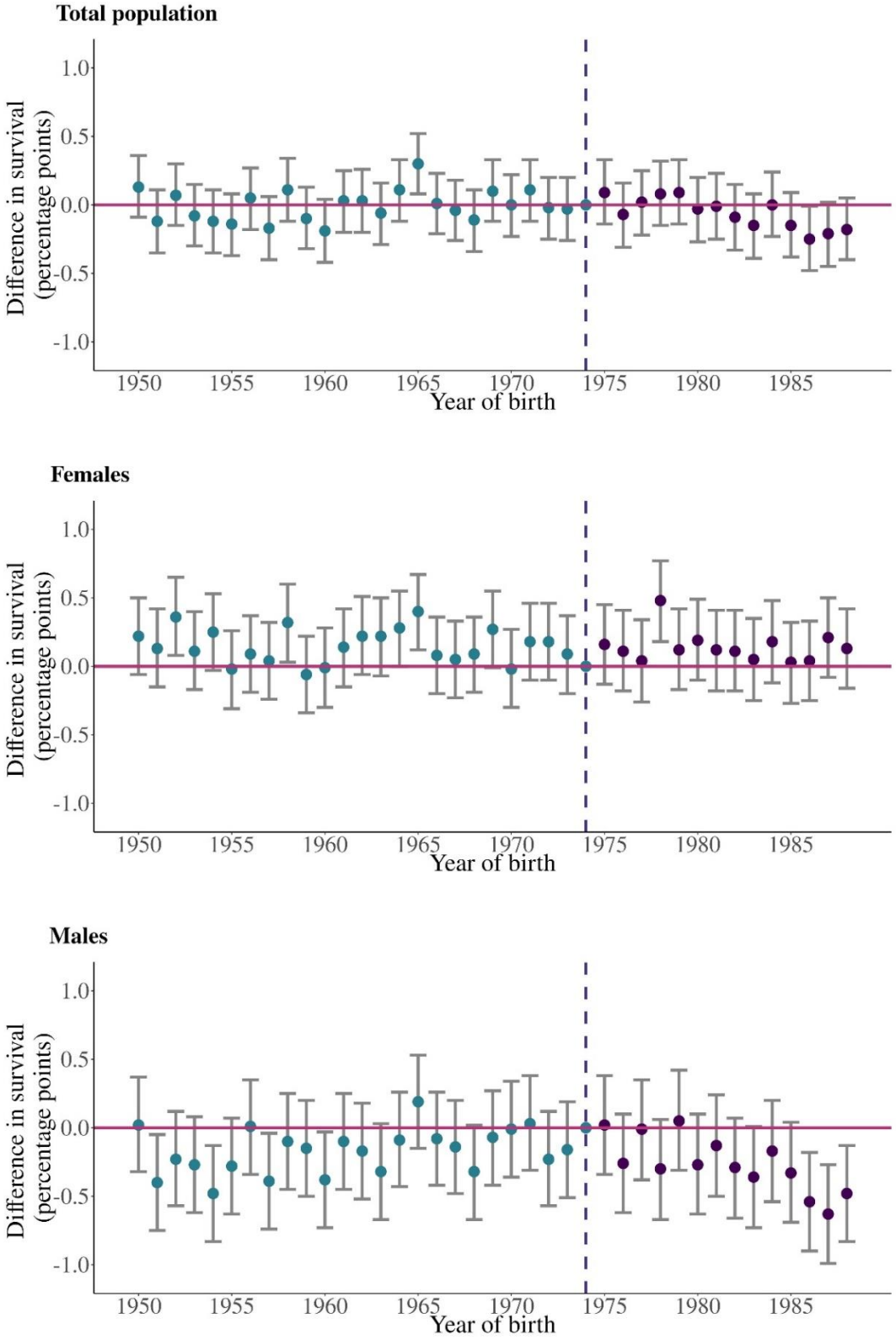
Source: mortality.org
Note: The vertical line is set at 1975, the year of the Bacillus Calmette–Guérin vaccine discontinuation.

Figure S 2: Log of survival to age 30 in Sweden



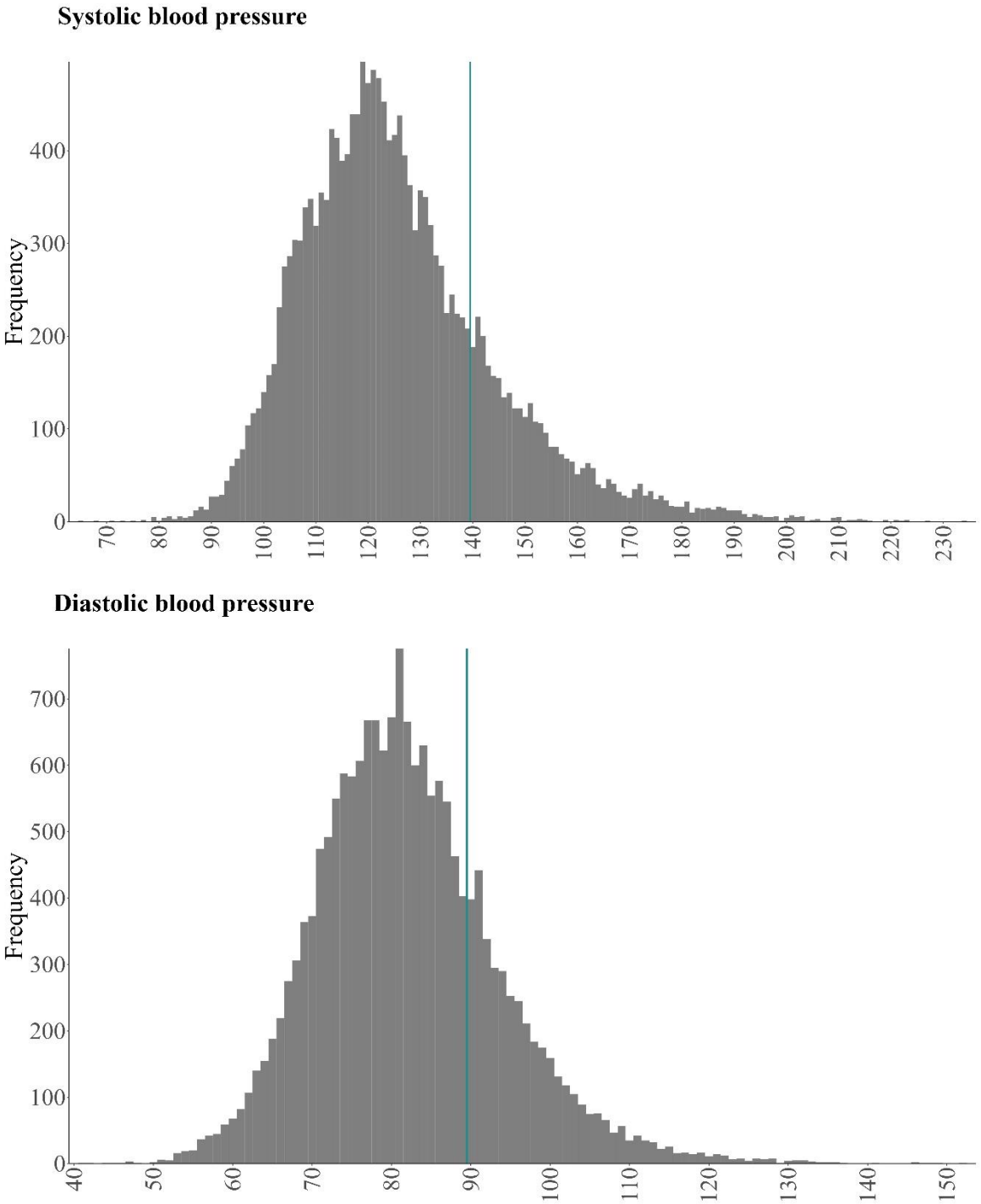
Note: The vertical line divides the birth cohorts into those born before the vaccine discontinuation (1975 and earlier) and those born after.

Figure S 3: Event study plot displaying multi-period Difference-in-Differences results; reference year: 1974



Note: Coefficients (with 95% confidence intervals) display the difference in the probability of survival between cohorts born in the respective year in Sweden and Norway net the secular time trend and fixed countries differences. The dashed vertical line marks the reference group, which is the cohort born in 1974.

Figure S 4: Frequency of each systolic and diastolic blood pressure measurement result among adults aged 30 years or older



Note: Frequency of each systolic and diastolic blood pressure measurement result among adults aged 30 years or older. The vertical line in the top panel marks the threshold at a systolic blood pressure of 140 mmHg and in the bottom panel at a diastolic blood pressure of 90 mmHg.