Population-Level Mortality Benefits of Improved Blood Pressure Control in Indonesia: A Parametric G-Formula Approach

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Abstract

Improving health and mortality in low- and middle-income countries (LMICs) is a major global policy goal. Policies and interventions that address high blood pressure (or hypertension) may be particularly promising for improving life expectancy in aging LMICs. However, direct estimates of the population-level mortality benefits of improved blood pressure control in LMICs remain unclear. Using nationally representative longitudinal data on Indonesian adults, I combine epidemiological and demographic modeling approaches to provide some of the first direct estimates of gains in adult life expectancy that would result from blood pressure reductions in a major LMIC. I consider both ideal scenarios as well as scenarios with imperfect control and compliance. I also investigate the distributional effects of blood pressure control by estimating the gains in life expectancy by quintiles of wealth. I find that bringing all individuals to ideal blood pressure levels results in a large, 5-6-year, improvement in adult life expectancy for both men and women. Life expectancy gains are more modest but still important under more realistic scenarios. Second, I find that the benefits of blood pressure control are not concentrated within any single wealth strata of the Indonesian population, but rather are equally distributed across rich and poor sub-populations. Based on the results of a simulation-based bias analysis, I find that even under high levels of unobserved confounding, the size of life expectancy gains from improving blood pressure control remains large. Overall, my results suggest that improving blood pressure control has the potential to greatly reduce mortality at the population level in Indonesia and other LMICs.

1. Introduction

Improving health and mortality in low- and middle-income countries (LMICs) is a major global policy goal[1]. To date, efforts to improve life expectancy in LMICs have focused heavily on reducing the high rates of infant and child mortality[2]. While under-five mortality remains high in many low-income countries (LICs), middle-income countries (MICs) are undergoing two important transitions that will shape how future mortality improvements are achieved. First, MICs are experiencing an epidemiological transition, where the burden of infectious diseases of childhood is giving way to a rising burden of chronic non-communicable diseases (NCDs) that primarily affect adults[3]. Second, MICs are also aging, increasing the share of both population and deaths in the older ages[4,5]. As these two transitions continue, an important question faced by MICs is what health conditions should be prioritized to efficiently improve life expectancy over the coming decades?

Policies and interventions that address hypertension (or high blood pressure) may be particularly promising for improving life expectancy in MICs. Contrary to common wisdom, hypertension is extremely prevalent in many MICs: recent studies find that the prevalence of hypertension among adults is between 30-70% in China, India, Indonesia, and Mexico[6,7]. The high prevalence of hypertension implies a substantial burden of mortality at the population level since hypertension greatly increases the risk of mortality from stroke, coronary heart disease, chronic kidney disease, and other cardiovascular diseases[8]. Hypertension also strongly increases with age[8] and will become more prevalent as MICs continue to experience population aging. Controlling hypertension is an appealing way to improve life expectancy for two additional reasons. First, hypertension is highly treatable and several clinical trials have demonstrated that daily, low-cost and low-side effect medications, can greatly reduce hypertension-related mortality[9]. Second, despite the high prevalence of hypertension and low cost of treatment, hypertension is largely uncontrolled in MICs[6,7]. Taken

together, blood pressure control can potentially result in large, population-level, improvements in mortality in MICs.

An additional important policy consideration is how the benefits of blood pressure control are distributed across the population. Explicitly or implicitly, many health policies aim to prioritize conditions that affect disadvantaged groups[1]. Hypertension and other NCDs are sometimes assumed to be "lifestyle diseases" or "diseases of affluence" that disproportionately affect the urban elite in LMICs—potentially reducing enthusiasm for hypertension prevention and control policies. However, an emerging body of evidence refutes this assumption. High levels of hypertension and hypertension-related mortality are found among populations that are poor, rural, lean, physically active, and largely consume traditional diets[10–12]. One common finding in these studies is that although levels of hypertension are comparable among socioeconomic (SES) groups, lower SES individuals are far less likely to be aware that they are hypertensive[10,13]. Therefore, improving blood pressure control may actually be more important for the poor compared to the rich.

Hypertension is strongly related to mortality, widespread in LMICs, and less diagnosed among the poor. These facts, combined with the relatively low cost of blood pressure medication suggest, that controlling blood pressure has the potential to be a cost-effective way of achieving large and equitable improvements in mortality at the population level. However, direct estimates of the population-level mortality benefits of improved blood pressure control in LMICs remain unclear, likely due to a paucity of representative microdata sources. Existing studies in this area rely on a combination of modeled and indirect estimates. In general, these studies find that among several modifiable risk factors (including tobacco use, alcohol use, blood pressure, blood glucose, unhealthy weight, and salt intake) blood pressure is among one of the greatest contributors to adult mortality in many regions of the world[14,15]. However, these estimates suffer from important limitations. First, they are based on indirect and modeled estimates, calling into question their validity for specific countries

and populations. In addition, they do not consider the gains that would result under more realistic scenarios, such as limited blood pressure control or control only among a subset of hypertensive individuals. Finally, they do not speak to the social or subnational distribution of benefits, such as whether the benefits are disproportionately clustered among richer or poorer individuals.

This study addresses these three gaps in our knowledge both substantively and methodologically. Substantively, I estimate the gains in life expectancy that would result from improving blood pressure control in Indonesia and identify how these gains are distributed across the population. I consider both ideal scenarios as well as scenarios with imperfect control and compliance. This approach reveals the benefits of various blood pressure control scenarios in the population and whether the benefits are concentrated among wealthier individual (as is often assumed) or equally distributed across the population. Indonesia is an important context to study hypertension since it is the third most populous LMIC, is rapidly aging, and has extremely high rates of hypertension[5,13]. Therefore, estimating the population-level benefits of improved blood pressure control could help to set health policy priorities and inform health decision-making at national and sub-national levels. Methodologically, I address the challenge of directly estimating population-level counterfactuals by combining a recently developed causal inference method in epidemiology, known as the parametric g-formula[16], with more traditional demographic mortality models to generate adult life expectancies under different levels of blood pressure control. This approach exploits rich panel data with measured blood pressure information in Indonesia to generate population-level mortality counterfactuals in a context without comprehensive vital registration or cause of death data. I also adapt a bias analysis technique developed for individual-level estimates[17] to the population level to determine how much support I have for giving my results a causal interpretation.

My paper proceeds as follows. Second 2 provides a background on blood pressure and mortality and a brief overview of other methods used to estimate the population-mortality burden of

modifiable risk factors such as blood pressure. In Section 3, I describe the methods I use to estimate counterfactual life expectancies and to conduct the bias-analysis. Section 4 gives an overview of the data and main study variables. Section 5 provides the results of four analyses. First, I estimate how many years of life expectancy would be gained by bringing all adults to an ideal blood pressure level. While unrealistic, this approach provides a measure of the burden, or importance, of blood pressure in Indonesia. Second, I simulate more realistic scenarios, varying the levels of blood pressure control and population coverage. Third, I estimate how the benefits of blood pressure reductions are distributed across wealth quantiles in Indonesia. Finally, I assess the robustness of my results to potential omitted variables through a simulation-based bias analysis. I conclude in Section 7 with a discussion of my results and their implications for future research and policy.

2. Background

Blood Pressure and Mortality

High blood pressure, also known as hypertension, is based on measurements of two different types of blood pressure: systolic and diastolic (both measured in millimeters of mercury or mmHg). Systolic blood pressure is the pressure blood exerts on the walls of the artery when the heart beats. Diastolic blood pressure is the pressure between beats. Individuals are typically classified as hypertensive if they have a systolic blood pressure greater than or equal to 140 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg.

Despite the high global prevalence of hypertension, the causes of hypertension remain poorly understood. Most cases of hypertension are classified as "essential" hypertension, or hypertension that is not the result other health conditions. However, the results from observational studies and clinical trials have identified a few important causal factors: age, weight, dietary factors (this includes both sodium consumption and other micronutrient deficiencies, physical inactivity, and genetic factors[18].

While studies find associations between more distal social exposures such as stress and socioeconomic status[19,20], it is less clear that these relationships are causal. Age, in particular, has a very strong association with blood pressure (especially systolic blood pressure). In the absence of blood pressure control, blood pressure rises steeply and linearly with age across populations and over time[8,21]. Increases in blood pressure with advancing age are also much larger than decreases in blood pressure produced through weight reductions, dietary changes, and physical activity improvements.

Hypertension increases the risk of mortality through several different causes of death, the most prominent of which is stroke[2]. Hypertension can damage blood vessels in the brain, making them more susceptible to bursting or rupturing (this is known as a hemorrhagic stroke). Hypertension is also related to a narrowing and clogging of blood vessels in the brain, reducing blood flow and making the brain more susceptible to clots (ischemic stroke). Both of these pathways lead to mortality by killing brain cells in the region of the rupture or clot. While stroke is the most common cause of death attributed to hypertension, elevated levels of blood pressure also cause mortality through coronary heart disease, chronic kidney disease, and other cardiovascular diseases. For example, high blood pressure can damage arteries leading to the heart, increasing the risk of blood clots that block flow to the heart, increasing the risk of heart attacks. Similarly, increased pressure in the blood vessels of the kidney can cause damage that hinders the ability of the kidney to clean blood—ultimately increasing the risk of kidney failure and mortality. While elevated levels of both forms of blood pressure can lead to mortality, the majority of the hypertension burden among adults is due to elevated systolic blood pressure.

Empirical evidence from multiple countries and periods confirms the biological relationship between blood pressure and mortality. Many studies find a continuous increasing relationship between

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[2] This paragraph is relies on Carretero et al. 2000,[41] which describes the etiology, consequences, and treatment procedures for hypertension.

blood pressure (especially systolic blood pressure) and mortality. For example, a meta-analysis of 61 prospective cohort studies concludes that a 20-mmHg increase in systolic blood pressure or a 10-mmHg increase in diastolic blood pressure is associated with a more than two-fold increase in stroke and ischemic heart disease mortality rates across all adult age groups[8]. Conversely, the results from numerous clinical trials have found that lowering blood pressure through a combination of medication and lifestyle treatments can drastically reduce the risk of blood pressure-related mortality. A meta-analysis of 112 blood pressure lowering trials finds that a 10-mmHg reduction in systolic blood pressure causes a 13% reduction in all-cause mortality regardless of baseline systolic blood pressure[22]. Emerging evidence suggests a near linear relationship between blood pressure reductions and mortality: a meta-analysis of 42 blood pressure clinical trials finds that individuals who reduced their systolic blood pressure down to 120-124 mmHg had 27% lower all-cause mortality compared those who achieved a blood pressure of 130-134 mmHg, 41% lower than those with a blood pressure between 140-14 mmHg, and 53% lower than those with a blood pressure of 160 mmHg or more[23]. Similarly, the recent systolic blood pressure intervention trial (SPRINT) finds that reducing systolic blood pressure to a target of less than 120 mmHg results in 27% lower all-cause mortality compared to a target of less than 140 mmHg[24].

Blood pressure can be reduced through several different medications and treatment combinations. An important question is whether all treatments confer the same mortality-reduction effects. Law et al. (2009) conduct a meta-analysis of 147 randomized trials to determine the relative efficacy of several alternative blood pressure treatments. Comparing across clinical trials that used different classes of medications, the study finds that for all but a subset of individuals (those with preexisting coronary heart disease), all the drug classes have similarly strong effects on mortality[9]. Law et al. conclude that the size of blood pressure reductions are ultimately what cause mortality reductions regardless of how the reduction was achieved. They subsequently compare the size mortality effects

of medically induced blood pressure changes to observed differences across individuals in cohort studies and find that the reductions in mortality from BP trials map very closely to observed differences in mortality for people at different levels of blood pressure. This insight is powerful and forms the basis of my estimation strategy for understanding the effects of different blood pressure control strategies since it implies that medication effects can be approximated by adjusted comparisons of individuals at different levels of blood pressure (this is related to the epidemiological notion of consistency discussed later).

Prevalence and Awareness of Hypertension in LMICs

While many studies have established the salience of hypertension for individual survival, they do not easily inform population health priorities. This is because individual-level risk estimates do not account for the prevalence and distribution of hypertension in a population. For example, if hypertension substantially increased the risk of mortality but was not very prevalent, then policies aimed at controlling blood pressure would not produce large gains in longevity at the population level. In contrast, if some other condition displayed a weaker individual-level relationship with mortality but was far more prevalent, treating this condition could potentially produce far greater population-level gains in longevity. Although high blood pressure is often believed to be a condition of high-income, populations, many studies document high levels of hypertension in less developed contexts[6,7,12,13,25,26].

Using data from the World Health Organization Study on Global Ageing and Adult Health (SAGE), Lloyd-Sherlock et al. (2014) find that the prevalence of hypertension among adults over the age of 40 is 57.1% in Ghana, 32.3% in India, and 58.2% in Mexico[7]. Similarly, Lu et al. (2017) find that 44.7% of adults ages 35+ in China are hypertensive and Berry et al. (2017) find that 35.1% percent of adults over the age of 15 are hypertensive in South Africa[6,27]. Hypertension and hypertension-related mortality are also not clustered within richer segments of the population within LMICs: in Malawi, the prevalence of uncontrolled hypertension is greater than 40% among the rural poor and

hypertension-related stroke is the leading cause of death in one of the poorest districts of rural Maharashtra, India[11].

Despite high levels of hypertension, levels of awareness of hypertension are very low in LMICs. For example, less than half of individuals in Ghana, India, South Africa, Mexico, and China are aware that they are hypertensive[6,7,27]. Indonesia follows this general pattern with very high levels of hypertension coupled with low levels of blood pressure awareness, treatment, and control. Hussain et al. (2016) find that nearly 50% of individuals above the age of 40 in Indonesia have hypertension yet only 30% of these individuals are aware of their hypertension. Levels of awareness of hypertension are even lower for individuals from poorer wealth quintiles (based on authors calculations with the Indonesian Family Life Survey). While around 70% of these individuals report taking medication, less than 25% achieved blood pressure control[13]. Hypertension is also not a recent phenomenon in Indonesia: Witoelar et. al. (2009) show that these levels have remained virtually unchanged since 1997[28].

Approaches to Measure the Population-Level Mortality Burden of Hypertension

Based on evidence presented in the previous two sections, hypertension is widely prevalent in LMICs and strongly increases the risk of mortality at the individual level. Taken together, these results imply that hypertension carries a large population-level burden of mortality. Yet direct estimates of the population-level mortality burden of hypertension in LMICs (measured either in years of life expectancy gained or the share of mortality attributable to hypertension) remain unclear. Part of the reason for the dearth of direct evidence is likely due to a lack of adequate data. Estimating the burden of hypertension requires either representative information on deaths due to different causes or microdata with measured blood pressure and adequate mortality follow-up. Since both of these sources of data are limited in LMICs, current measures of population burden in these contexts are based on indirectly or heavily modeled approaches[14,15,29].

Currently, the most widely used measure of population mortality burden in LMICs is the population-attributable fraction (PAF) (PAFs are also known as the population impact fractions (PIF)). The PAF measures the proportional change in mortality (measured either in rates or counts) in a specific age-range that would occur if the level of a risk factor was reduced to some target level[30]. Estimating the PAF requires estimates of the distribution of each risk factor within a population, the mortality rates in a population, and the effect of the risk factor to be evaluated on mortality. Given the relative paucity of direct data with this information (until recently), the most prominent and widely cited PAF estimates in LMICs are indirectly estimated using modeled risk factor distributions, modeled mortality rates, and effect estimates drawn from meta-analyses, small-scale epidemiological studies within countries, and studies from other contexts. The evidence from these studies suggest a large population level-burden of high blood pressure in LMICs: for the African, Southeast Asian, and Western Pacific regions of the world, reducing blood pressure would provide the largest reduction in adult mortality among eight risk factors considered for women, and the second largest reduction for men (after tobacco use)[14]. These studies are instructive for broad stylized facts but suffer from a few important limitations. First, since nearly every input is modeled or drawn from other populations, the validity of the estimate for any specific population is unclear. Second, while theoretically possible with PAF approaches, current estimates do not display the population-level mortality effects of more nuanced and realistic scenarios, such as "how many years of life expectancy would be gained if 20% of hypertensive individuals were able to reduce their systolic blood pressure by 10 mmHg?". Given that policies are often crafted with limited budgets, understanding the health benefits of less than perfect control scenarios is important for priority setting. The third major limitation is that these measures do not provide information on the social distribution of benefits within a country (e.g. are the gains in life expectancy from hypertension treatment equally distributed across socioeconomic groups or does the burden of hypertension disproportionately affect some sub-populations?). Since

the goal of many health policies is to maximize equity in addition to improving population health, current estimates are less than ideal for policy decision making.

Studies based on data from HICs often use microsimulation models to estimate PAF and PAF-like policy counterfactuals. For example, the IMPACT model developed by Capewell et. al. (1998) combines information on trends in population-level risk factors with information on the relationship between risk factors and outcomes to decompose changes in coronary heart disease mortality over time into the contribution of changes in specific risk factors[31]. These types of models can also be applied prospectively to generate policy counterfactuals: Capewell et al. (2010) apply the IMPACT model prospectively to the US population for the year 2000 and conclude that half of coronary heart disease deaths could be averted by 2010 if the population were to achieve the Healthy People 2010 goals (no smoking, lowered total cholesterol, lowered blood pressure, and lowered body mass index)[32].

My paper follows the spirit of both the aggregate PAF approach and the microsimulation IMPACT model. However, I provide a number of new contributions to existing work in this area. First, I use rich nationally representative microdata with measured blood pressure information and mortality follow up to generate some of the first direct estimates of the population mortality burden of hypertension for a major middle-income country (Indonesia). Second, I generate more nuanced policy-relevant counterfactuals varying both the levels of blood pressure reduction and the percent of hypertensive individual that successfully reduce their blood pressure. I estimate these counterfactuals by adapting a simulation-based reweighting technique developed in epidemiology (known as the parametric-g formula[16]) with demographic modeling approaches to simulate the consequences of different levels of blood pressure policy coverage and control on years of life expectancy gained. Third, I take advantage of individual-level data to estimate the gains in life expectancy across the wealth

distribution of Indonesia—this approach is especially important for considerations of equity since it identifies how the benefits of blood pressure control are distributed across the population.

3. Estimation Approach

The main empirical goal of this paper is to estimate how many years of adult life expectancy are gained under different levels of blood pressure control. I describe my approach in detail below but briefly summarize it here. To begin, I first estimate the individual-level relationship between blood pressure and age-specific mortality using longitudinal microdata from Indonesia. I then set a counterfactual blood-pressure level for a subset of hypertensive individuals and use a simulation-based reweighting technique (known as the parametric g-formula[16,33]) to aggregate the individual-level effects to the population level under the various blood pressure reduction scenarios. I then construct period life tables using the counterfactual age-specific mortality rates to estimate counterfactual adult life expectancies. Finally, I estimate the gains in life expectancy as the difference between observed life expectancy and the various counterfactual life expectancies. Throughout this exercise, I adopt a counterfactual and potential outcomes-based perspective to express and estimate the individual and population-level effects. This approach explicitly specifies the causal question of interest and identifies which quantities are observed and which are counterfactual. Another important advantage of the counterfactual formulation is that it leads to an analytical expression for the effect of unobserved confounding on the estimates. Using this expression, I simulate the consequences of endogeneity on my estimates of life expectancy years gained to determine how much support there is for a causal interpretation of my results.

Scenario 1: Full Control of Systolic Blood Pressure

I first estimate how many years of adult life expectancy would be gained if all individuals brought their systolic blood pressure to an ideal level (defined as a systolic blood pressure as 125 mmHg based on

the results from recent clinical trials[24]). My main results are based on a continuous measure of systolic blood pressure; however, I describe the approach here for a dichotomous indicator for whether an individual is hypertensive. This is primarily for ease of exposition—the approach conceptually generalizes to a measure of continuous blood pressure case at the cost of far more cumbersome notation.

To begin, consider data that are at the person-age level (e.g. individuals have one observation for each age), with an indicator for whether the individual is hypertensive, an indicator for whether the individual died during that age, and a continuous measure of the exposure time lived in the interval (this would be equal to 1 if the individual survived the entire year). Estimates based on this data setup correspond to single-age annualized rates or probabilities. Now define, D_{ijk} as a Poisson random variable that takes the value of 1 if an individual k of sex j dies between ages i and $i+1$ and 0 otherwise. Since the age-specific count of deaths is influenced by the size of the population in that age range, estimates of mortality are usually normalized into rates by dividing by the total person-time of exposure lived between the two ages. Let L_{ijk} be a fixed number between 0 and 1 that measures how much time and individual k of sex j and lived between ages i and $i+1$. Based on this setup, the average age-and sex-specific annual mortality rate in the population can be estimated as the expected count of deaths divided by the total person-time of exposure in the age range, $E(D_{ijk})/total(L_{ijk})$. For simplicity, call this quantity $E(M_{ij})$ (in life table calculations, this rate is often represented in as m_x or $_1m_x$).

To incorporate hypertension into the mortality rate, note that the age and sex-specific mortality rate can be expanded by conditioning on hypertension status (represented as H_{ij}, a Bernoulli random variable that takes the value of 1 if an individual of age i and sex j is hypertensive):

$$E(M_{ij}) = E(M_{ij}|H_{ij} = 1)P(H_{ij} = 1) + E(M_{ij}|H_{ij} = 0)P(H_{ij} = 0). \tag{1}$$

Expanding reveals that the age-sex-specific mortality rate is a weighted sum of the mortality rate of the normotensive ($H=0$) and the hypertensive ($H=1$). Now consider the counterfactual scenario

where everyone in the population remains the same except that all hypertensive individuals are brought to the normotensive blood pressure range. Define the age- and sex-specific mortality rate that results under this counterfactual scenario as $E(M_{ij}^*)$ and explicitly reveal the potential outcomes by conditioning on hypertensive as done above:

$$E(M_{ij}^*) = E(M_{ij}[H_{ij} = 0]|H_{ij} = 0)\Pr(H_{ij} = 0) + E(M_{ij}[H_{ij} = 0]|H_{ij} = 1)\Pr(H_{ij} = 1). \qquad (2)$$

Here, the statement in brackets after M represents setting hypertension to the specified value; for example, $E(M_{ij}[H_{ij}=0]|H_{ij}=0)$ is the average mortality rate for those without hypertension if they were set to not having hypertension (this potential outcome can be observed). Conditioning on hypertension status reveals that $E(M_{ij}^*)$ is a weighted sum of the mortality rate for those who do not have hypertension, $E(M_{ij}[H_{ij}=0]|H_{ij}=0)$, and the mortality rate for those who do have hypertension if they were instead set to normotensive, $E(M_{ij}[H_{ij}=0]|H_{ij}=1)$ (in the individual-level treatment effects literature, this term is often referred to as the average treatment effect on the treated [ATT]). This formulation reveals that $E(M_{ij}^*)$ is a combination of both an observed and counterfactual potential outcome since the potential outcome $E(M_{ij}[H_{ij}=0]|H_{ij}=1)$ is not observable.

One approach to recovering this potential outcome is to find a set sufficient set of covariates $X_1,…,X_n$ such that:

$$E(M_{ij}[H_{ij} = 0]|H_{ij} = 1, X_1, …, X_n) = E(M_{ij}|H_{ij} = 0, X_1, …, X_n). \qquad (3)$$

Assuming these variables exist and are observable (the bias analysis procedure outlined later in this section seeks to evaluate the support for this admittedly strong assumption), the unconditional potential outcome needed to construct $E(M_{ij}^*)$ can be estimated by "integrating out" the X variables. In practice, this is done by estimating the conditional mortality rate for each combination of all the X variables when $H_{ij}=0$, multiplying by the marginal probability of that specific combination of X's among the hypertensives, and then summing over all observed combinations of the X's. In epidemiology and biostatistics this approach is known as the non-parametric g-formula and is

essentially a form of multivariate direct standardization[16]. For the sake of clarity collapse all the X's into one confounder C with values $\{1,\ldots,K\}$ representing all strata of the joint distribution of $X_1,\ldots,X_n$. This estimation approach can now be analytically represented as:

$$\hat{E}\big(M_{ij}[H_{ij} = 0]|H_{ij} = 1\big) = \sum_{C} \hat{E}\big(M_{ij}|H_{ij} = 0, C_{ij} = k\big)\hat{P}\big(C_{ij} = k|H_{ij} = 1\big). \tag{4}$$

Once this potential outcome is estimated, the rest of $E(M_{ij}^*)$ can be constructed by directly estimating the other observed quantities from the data:

$$\hat{E}\big(M_{ij}^*\big) = \hat{E}\big(M_{ij}|H_{ij} = 0\big)\,\hat{P}\big(H_{ij} = 0\big) + \hat{E}\big(M_{ij}[H_{ij} = 0]|H_{ij} = 1\big)\hat{P}\big(H_{ij} = 1\big) \tag{5}$$

where

$$\hat{E}\big(M_{ij}[H_{ij} = 0]|H_{ij} = 1\big) = \sum_{C} \hat{E}\big(M_{ij}|H_{ij} = 0, C_{ij} = k\big)\hat{P}\big(C_{ij} = k|H_{ij} = 1\big). \tag{4}$$

While this quantity could be estimated based on the specification in equation (5), the number of strata of C becomes extremely large as the size of the covariate set increases. The increasing dimensionality can result in many strata in the sample with no observed normotensive individuals. One solution to this problem is to specify a parametric model for $E(M_{ij}|H_{ij},X_1,\ldots,X_n)$, resulting in the procedure known as the parametric g-formula[16]. Specifically, for a set of observed covariates $X_1,\ldots,X_n$, I estimate the following Poisson regression model:

$$\ln\big(E(D_{ij})\big) = \beta_0 + \beta_1 Age + \beta_2 H + \sum_{i=1}^{n} \gamma_i X_i + \ln(L_j). \tag{6}$$

There are two important things to note with this model: first, mortality rates are modeled by taking the count of deaths (D_{ij}) as the outcome with the person-years of exposure included as an offset. Second, age is now a covariate in the model, resulting in only models separate by sex, rather than sex and age. As previous, represent all the X's as single composite variable C. To then estimate $E(M_{ij}[H_{ij}=0])|H_{ij}=1)$ using the parametric g-formula, substitute the model predicted rates into the non-parametric expression above (4):

$$\hat{E}(M_{ij}[H_{ij} = 0]|H_{ij} = 1) = \sum_{k=1}^{C} \exp(\hat{\beta}_0 + \hat{\beta}_1 i + \hat{\gamma}_k k) \, \hat{P}(C = k|H_{ij} = 1, Age = i, Sex = j) \qquad (7)$$

Note that the value of the offset, *L,* is set to one for all strata, resulting in an estimate of deaths per person-year of exposure. This estimate can now be subbed back into equation (5) to form an estimate of $E(M_{ij}^{*})$.

At this point, the population-level mortality benefits of hypertension control could be estimated by directly comparing differences in the observed and counterfactual age-specific mortality rates. However, interpreting differences in rates over a wide range of ages is difficult. For this reason, sets of age-specific mortality rates are often summarized as a period life expectancy, or the average number of years an individual would live if they were exposed over the remainder of their lives to the observed age and sex-specific mortality rates. This approach moves beyond estimating the effect of hypertension on mortality rates to a more interpretable contrast of the effect of hypertension on adult life expectancy (in this case, life expectancy at age 40). I follow this convention by using standard period life table techniques to construct life expectancies at age 40 for the observed and counterfactual scenarios. Assuming unbiased life expectancy estimates for each counterfactual, the gains in life expectancy for each blood pressure scenario is the difference between the observed and counterfactual life expectancies.

Scenario 2: Partial Control and Compliance

In the second part of my analyses, I consider more realistic scenarios, varying both the size of blood pressure reductions and the proportion of hypertensive individuals that successfully reduce their blood pressure. Estimating gains in life expectancy from different magnitudes of systolic blood pressure reductions follows directly from the exposition above. However, varying the proportion of individuals that successfully reduce their blood pressure is not as straightforward and requires a simulation-based method.

First, consider modeling a continuous measure of systolic blood pressure rather than a dichotomous indicator for hypertension status. The observed mortality rate is now represented as:

$$E(M_{ij}) = \sum_{BP} E(M_{ij}|BP_{ij} = bp)P(BP_{ij} = bp) \tag{8}$$

Now suppose that we want to evaluate the effect of a policy to lower systolic blood pressure by 10 mmHg for all individuals with a systolic BP greater than 140 mmHg (the traditional hypertensive cutoff). Analytically, this can be represented by:

$$E(M_{ij}^*) = E(M_{ij}|BP_{ij} < 140mmHg)P(BP_{ij} < 140mmHg) +$$

$$\sum_{BP|BP \geq 140} E(M_{ij}[BP_{ij} = bp - 10]|BP_{ij} = bp)P(BP_{ij} = bp) \tag{9}$$

There are now potential outcomes corresponding to each systolic BP value above 140. Empirically, $E(M_{ij}^*)$ can now be estimated using a similar procedure as described above by first estimating a Poisson regression with systolic blood pressure as the main exposure, re-predicting mortality with systolic blood pressure values that are 10 units below the observed values for hypertensive individuals, aggregating these counterfactual potential outcomes across the strata of X variables, and finally forming the counterfactual mortality rate by weighting each blood pressure-specific mortality estimate by the share of the population in each blood pressure bin.

This step reveals how to estimate gains in mortality under different levels of blood pressure reduction but it still assumes that reductions happen for all individuals with a BP greater than 140. What if, for example, only 20% of hypertensive individuals were able to achieve those blood pressure reductions? An obvious solution might be to only assign blood pressure reduction to 20% of hypertensive individuals; however, which 20% of individuals are chosen affects the resulting estimate since non-linear models (like a Poisson regression) are multiplicative with respect to other covariates. Conceptually, one way to address this issue to average over all possible combinations that can be obtained by randomly assigning 20% of hypertensives to blood pressure reductions. This solution can

be empirically approximated using simulations by creating Q copies of the original data, randomly assigning blood pressure reductions to 20% of hypertensive individuals separately for each $q \in Q$, estimating the counterfactual mortality rate for each $q \in Q$, and finally averaging the counterfactual rates over all Q (this entire procedure is a form of the parametric g-formula[16,33]). Combining the simulation-approach to varying the share of hypertensives that reduce their blood pressure with a range of obtained blood pressure reductions provides a picture of potential gains under a wide range of more realistic scenarios.

Bias Analysis

The estimated gains from the previous approaches will only be an unbiased estimate of the true causal effects of blood pressure reductions under the strong assumption that the exposure status (systolic blood pressure) is conditionally independent of the potential outcomes given C. That is, conditional on the set of observed covariates C, the coefficient estimate on systolic blood pressure represents the causal effect of blood pressure on mortality. If there were unobserved confounders, collapsed here into a single variable U, then the estimate would only be unbiased conditional on U.

$$E\left(M_{ij}[BP_{ij} = bp^*])\middle|BP_{ij} = bp, X_1, \dots, X_n, U\right) = E\left(M_{ij}\middle|BP = bp^*, X_1, \dots, X_n, U\right). \tag{10}$$

This implies that when U is not conditioned on:

$$E\left(M_{ij}[BP_{ij} = bp^*]\middle|BP_{ij} = bp, X_1, \dots, X_n,\right) \neq E\left(M_{ij}\middle|BP_{ij} = bp^*, X_1, \dots, X_n,\right). \tag{11}$$

By making a few assumptions about the structure of U, I can assess the robustness of my estimated effects to different levels of unobserved bias. I first consider an intervention to reduce blood pressure by 20 mmHg for those with a systolic blood pressure $\geq$ 140 mmHg. I then assume that the relationship between U and mortality does not vary based on the levels of the other covariates and that the difference in the prevalence of U associated with a 20-mmHg change in systolic blood

pressure is the same in all strata of C. Then, the bias B (expressed as the difference between the true and estimated effect) is:

$$B = \{P(U_{ij} = 1|BP_{ij} = bp^*, X) - P(U_{ij} = 1|BP_{ij} = bp^* - 20, X)\} * \{E(M_{ij}|BP_{ij}, X, U_{ij} = 1) - E(M_{ij}|BP_{ij}, X, U = 0)\}. \tag{12}$$

This formulation reveals that the degree of bias can be expressed as a product of the difference in the prevalence of the unobserved confounder associated with a 20-mmHg change in systolic blood pressure (the relationship between the confounder and hypertension) and the difference in the probability of mortality for those with and without the unobserved variable (the relationship between the confounder and mortality). For a proof of this formula see:[17]. Within this structure, the unbiased estimate of the age-specific counterfactual mortality rate is given by (representing the biased estimate of the counterfactual potential outcome as $E(M^{**})$):

$$\hat{E}(M_{ij}^*) = \hat{E}(M_{ij}|BP_{ij} < 140mmHg)\hat{P}(BP_{ij} < 140mmHg) +$$

$$\sum_{BP|BP \geq 140} (\hat{E}(M_{ij}^{**}|BP_{ij} = bp) + B)\hat{P}(BP_{ij} = bp) \tag{13}$$

By setting different values of the two sensitivity parameters, adding the bias to the estimate of the counterfactual potential outcome, re-computing the counterfactual age- and sex-specific mortality rates, and then estimating counterfactual life expectancies with the bias adjusted rates, I can see how my estimate of the effect of blood pressure reduction on life expectancy varies under different levels of unmeasured confounding. Importantly, this approach does not solve the causal identification problem; rather, it provides a heuristic to evaluate the support for a causal interpretation of the findings by first seeing how much bias there would have to be to invalidate the conclusions drawn from the estimates and then asking if those levels of bias are plausible or likely to exist.

A second, subtler, assumption needed for a causal interpretation is that the difference in mortality across individuals at different levels of blood pressure represents the change in mortality that would occur from lowering the blood pressure of any given individual through a hypothesized

treatment (this is referred to as consistency in epidemiology). If the damage of high blood pressure was only partially reversible, then the mortality of an individual with a lower blood pressure would not represent the counterfactual mortality of a high blood pressure individual if they lowered their BP. However, results from the Law et al. (2009) study provide support for consistency, demonstrating that the effect of medically induced blood pressure changes can be approximated by differences across individuals[9].

4. Data and Variables

Data

Data are from the 2007 and 2014/2015 waves of the Indonesian Family Life Survey (IFLS)[34,35]. The IFLS is a longitudinal survey of individuals and households from 14 of Indonesia's 34 provinces (the IFLS is representative of 83% of Indonesia's population). The IFLS contains detailed information on health and socioeconomic conditions as well as a host of measured biomarker and anthropometric data. This analysis is limited to target respondents above the age of 40 (other members in the household were sometimes also measured but since they were not explicitly followed-up in the 2014/2015 wave, I cannot construct reliable estimates of mortality for these individuals). Among 11,895 target individuals, 782 individuals were dropped for missing blood pressure information (6.6% of the total eligible sample) and an additional 1,028 individuals were dropped for missing information on the other covariates (9.3% of the remaining eligible sample) for a total sample size of total sample size of 10,085 individuals with 75,288 person-age observations (85% of the eligible sample).

Primary Outcome

The primary outcome is mortality. If an individual died between survey waves, a close household member was asked to report their month and year of death. Together with information on date of birth and date of interview in the 2014/2015 wave (for those that survived), I generate person-year

observations for every individual surveyed in the 2007 wave. For example, if an individual was born in January 1960, was surveyed in February 2007, and died in March 2010, I would create 5 person-age observations for the individual corresponding to the ages 47, 48, 49, and 50. Additionally, this individual would be marked as alive with a full person-year of exposure for the ages 47, 48, and 49 and be marked as having died at age 50 with two months of exposure. If this individual did not die but rather was interviewed again in March 2015, I would create 9 person-age observations for the years 2007-2015, censoring the age attained in 2015 by assigning that age an exposure of 2 months. The IFLS has excellent tracking follow up for target respondents and the mortality status of all target individuals in the 2007 wave was known in 2014/2015. Appendix Table 1 shows the age and death distribution of the sample based on age at baseline in 2007.

Primary Exposure

The primary exposure in this study is systolic blood pressure. For each individual, three separate measures of blood pressure were taken by a trained assessor using an Omron HEM-7203 device. Following the World Health Organization procedure, I average the second and third measurement, omitting the first measurement. In alternative analyses, I present results for a dichotomous classification of hypertension. For these analyses, individuals were classified as hypertensive based on National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure cutoffs (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg)[36].

Other covariates

My empirical approach requires identifying and controlling for a set of covariates that make the assignment of systolic blood pressure conditionally independent from the potential outcomes. Based on prior studies on potential causes of blood pressure and mortality[18,37], I identify the following set of covariates that encompass both proximate and distal potential causes of blood pressure and mortality:

urban or rural residence (based on census classification); province of residence (dummy variables for each province); religion (grouped into Islam, Hindu, Protestant, and other); marital status (grouped into never married, current married, and formerly married); self-reported occupation type (grouped into retail, manufacturing, agriculture, service, housewife, retired, and not working); self-reported completed schooling (grouped into no schooling, some primary school, primary school or more); wealth quintiles (constructed using principle components analysis on indicators for asset ownership); body mass index (measured continuously as height in meters divided by weight in kilograms squared), and the average number of days a week an individual engages in moderate or vigorous physical activity. Diet may also be an important confounder but diet information is extremely limited in the IFLS. However, assuming that diet is mostly determined by social and environmental influences, conditioning on the socioeconomic and geographic covariates included would control some part of the effect of diet.

Around 20% of hypertensive individuals report taking some form of medication for blood pressure. Based on the results of Law (2009), the measured blood pressure of these individuals is the most important determinant of their blood-pressure-related mortality risk[9]. For this reason, I include individuals who report taking some medication, focusing on their measured blood pressure as the primary exposure. In alternative analyses, I both exclude these individuals and control for treatment in the analyses and find no substantive change to my conclusions.

5. Main Results

Descriptive Results

Table 1 presents descriptive characteristics of the sample for the baseline 2007 wave. The mean age of the sample was 53.6 years. The sample was split evenly between men and women (52.5% female) and urban/rural (50.3% urban). The vast majority of individuals were married at baseline (80.3%) with

Islam as the primary religion (88.6%). Less than half of individuals had more than primary schooling (48.1%) with agriculture and retail as the most common occupations (31.0% agriculture and 18.2% retail). The sample was on average normal weight (mean BMI of 23.0) and fairly active (on average individuals engaged in moderate of physical activity for 4.3 days in a week).

Figure 1 graphs the continuum of hypertension in Indonesia. Levels of hypertension are extremely high in Indonesia (45.2% of adults ages 40 and above are hypertensive). Despite these levels, only 34.4% of hypertensive individuals have been diagnosed. While 76.8% of diagnosed individuals reported taking hypertensive treatment, only 23.3% of those under treatment achieved blood pressure control. Across the full continuum only 6.2% of hypertensive individuals in Indonesia have controlled blood pressure.

The potential gains in life expectancy from controlling blood pressure depend on how blood pressure varies over age. Figure 2 graphs the age and sex-specific prevalence of hypertension (the trend is virtually identical for mean systolic blood pressure). For both men and women, hypertension rises very steeply with age: for men, the prevalence of hypertension starts around 28% at age 40 and reaches around 60% by age 75. The age-pattern of hypertension is steeper for women: by age 75, nearly 75% of women over have hypertension in Indonesia. An important caveat to these results is that they are based on cross-sectional data—therefore, differences across ages could also represent period- and cohort-specific influences.

Blood Pressure and Mortality

Table 2 presents the rate regression estimates of the relationship between blood pressure and mortality across three models separately by sex. The table presents coefficients for two forms of blood pressure, a dichotomous indicator for whether an individual is hypertensive and continuous measure of systolic blood pressure in 10 mmHg units. Subsequent analyses use the continuous measure but the dichotomous indicator is presented to provide an estimate of the importance of hypertension as

clinically defined. Model 1 only adjusts for age, model 2 adds a wide array of health and sociodemographic confounders, and model 3 includes province fixed effects. For both men and women, I find a strong relationship between hypertension and mortality that robust to the inclusion of a large set of potential confounders. Assuming for now that the observed estimates are unbiased, in the fully adjusted model hypertension increases the rate of mortality by 80% for men and 50% for women (RR: 1.8, 95% CI: 1.5, 2.2 for men; RR: 1.5, 95% CI: 1.2 – 1.9 for women). In systolic blood pressure units, I find that a 10 mmHg increase in systolic blood pressure is associated with a 16% (RR: 1.16, 95% CI: 1.11, 1.21) increase in mortality for men and a 13% (RR: 1.13, 95% CI: 1.09, 1.17) increase for women. These last estimates form the basis of the counterfactual analyses and are assumed to represent the causal effect of blood pressure changes on mortality. The bias analyses presented later in this section simulate the effects of departures from this assumption on the overall estimates of life expectancy years gained; however, it is reassuring that the regression estimates map very closely to the mortality effect of a 10 mmHg systolic blood pressure reduction found in clinical trials for blood pressure medications[22].

Full Control of Blood Pressure

The regression estimates capture the individual-level relationship between blood pressure and mortality but they do not readily reveal the importance of blood pressure at the population level. In Table 3, I present estimates of the gains in life expectancy from an ideal scenario where all individuals with a systolic blood pressure > 125 mmHg bring their blood pressure down to 125 mmHg. Full control of blood pressure results in a large, 5-6 year, improvement in mortality at the population level for both men and women. For men, controlling systolic blood pressure would move life expectancy at age 40 by 5.3 years (p<0.001) from 34.7 (95% CI: 33.8, 35.6) to 40.0 (95% CI: 37.6 43.7) years. The gain is slightly larger for women (6.0 years, p < 0.001), moving life expectancy at age 40 from 37.6

(36.5, 38.8) to 43.7 (40.6, 46.7) years. While full blood pressure control is an unrealistic policy goal, this exercise reveals a large population mortality-burden of high blood pressure in Indonesia.

Partial Control and Compliance

Figure 3 presents the gains in life expectancy from a more realistic set blood pressure control scenarios. Gains are shown across two dimensions, reductions in blood pressure from 5 to 20 mmHg, and the share of individuals that achieve blood pressure reductions ranging from 10% to 100% of those with a systolic BP > 140 mmHg (a standard screening threshold for determining whether an individual should be taking treatment). In contrast to the ideal scenario, the more realistic scenarios display far more modest improvements. For example, if 50% of hypertensive individuals reduced their systolic blood pressure by 15 mmHg, the gain in life expectancy for both men and women would be around 1 year. Life expectancy gains are much larger at the extremes of the scenarios but still well below the ideal scenario: if all hypertensive individuals reduced their blood pressure by 20 mmHg, there would be around a 2.5-year gain in life expectancy. While changes in life expectancy between 1 and 2.5 years are not trivial, the figure reveals that larger improvements in mortality may only be achieved by encouraging larger reductions in blood pressure among the very high-risk individuals (for example reductions in blood pressure of greater than 20 mmHg for individuals with a systolic blood pressure > 160 mmHg).

Distributional Effects of Blood Pressure Control

To determine whether the gains in blood pressure control are equally distributed across the population or concentrated among richer individuals, I first estimate the age-standardized prevalence of hypertension across wealth quintiles (Figure 4). For both men and women, I do not find evidence that the prevalence of hypertension is clustered in any specific wealth segment of the population. Levels of hypertension hover around 40% for men in all five wealth quintiles and range between 45-50% for

women. Contrary to the belief that hypertension is highest among wealthier individuals, the evidence here actually suggests that women in the poorest wealth quintile have the highest prevalence of hypertension (although the 95% confidence interval overlaps with the prevalence estimates for the other quintiles).

The gains in life expectancy by wealth quintile also depend on how the relationship between blood pressure and mortality varies across quintiles. In Appendix Table 2, I present the results from regressions of mortality on blood pressure with interactions by wealth quintile. In general, I do not find strong evidence that the relationship between blood pressure and mortality varies by wealth quintile (most of the interaction terms have p values well above 0.1). I do find marginal evidence that blood pressure is more strongly predictive of mortality for men in the richest wealth quintile ($p = 0.068$) but given the number of interaction terms this could plausibly be driven by chance.

Figure 5 plots the gains in life expectancy from the ideal blood pressure control scenario separately by wealth quintile and sex. The results mirror the trends in the age-standardized prevalence of hypertension: there is around a 5.5-year gain in life expectancy for men and women in all wealth quintiles. These results suggest that the benefits of blood pressure reductions are not isolated to any particular segment of the population.

Bias Analysis

The causal interpretation given to my estimates is predicated on the assumption of no unobserved variables (no residual confounding or endogeneity). If my observed result was driven by the influence of an unobserved confounder, then the estimates above may overstate the benefits of blood pressure control. In Figure 6, I assess the sensitivity of my estimate of life expectancy years gained to departures from my identifying assumption. I make a few assumptions to improve the interpretability of the results. First, I only consider a single intervention that reduces systolic blood pressure by 20 mmHg for all individuals with a systolic blood pressure ≥ 140 mmHg. Second, the role of all unobserved

variables is collapsed into a single binary confounder. The effect of this confounder on my estimate depends on two factors: how strongly this unobserved variable is related to mortality and how much more prevalent it is (net of all observed control variables) across systolic blood pressure.

In the absence of unobserved bias, I find that a 20-mmHg systolic blood pressure reduction results in around a 2.4-year gain in life expectancy at age 40 for both men and women. The sensitivity results reveal that the size of life expectancy gains is very robust to omitted variables. For example, if a 20-mmHg change in blood pressure increased the prevalence of an unobserved confounder by 40 percentage points (net of all controls) and increased the risk of mortality by 15%, the years of life gained would still be above 2 years for both men and women. Indeed, even under extreme levels of unobserved confounding, where a 20-mmHg blood pressure change increased the prevalence of the unobserved variable by 75 points and increased mortality by 25%, the proposed intervention would still result in around 1.4-1.6 years of life expectancy gained at the population level.

6. Discussion

The populations of many LMICs are projected to age dramatically over the coming decades. In the backdrop of population aging, identifying which health conditions will provide the largest gains in well-being at the population level is important for setting health priorities and informing decision making at the global, national, and subnational levels. Hypertension is already a leading risk factor for mortality in many LMICs[38] and will only increase in prevalence as the share of older individuals grows. I combine epidemiological and demographic modeling approaches to provide some of the first direct estimates of gains in adult life expectancy that would result from blood pressure reductions in a major LMIC.

As a measure of the burden of high blood pressure, I first consider a scenario where all individuals achieve ideal blood pressure levels and find extremely large, 5-6 year, improvements in

adult life expectancy for both men and women. The size of this change is substantial: as a reference, a 5 change in life expectancy at 40 corresponds to the difference between life expectancy at age 40 in Indonesia between 1950 and 2010, or equivalently, 60 years of progress in improving adult mortality. This finding is striking for revealing the burden of hypertension in Indonesia but reflects the result of a blood pressure thought experiment rather than a plausible policy outcome. The results from more realistic blood pressure scenarios are far more modest: under plausibly attainable levels of blood pressure reductions and compliance, life expectancy gains range between 1 and 2.5 years. While 1-2.5 year improvements are non-trivial at the population level, these results also highlight the need to investigate alternative strategies for blood pressure reductions. Selectively targeting high-risk individuals, such as those with a systolic blood pressure > 160 mmHg, and encouraging larger gains may be an important corollary to broad population blood pressure control policies. These types of hybrid approaches may result in life expectancy improvements that are closer to the ideal control scenario. Combining blood pressure care with other health policies, such as tobacco cessation, might also provide a strong approach to efficiently improve adult mortality at the population level.

Beyond overall population health, the goal of many health policies is to improve health equity by addressing conditions that are salient among vulnerable populations. I find that the high prevalence of hypertension is not concentrated within any single wealth-strata of the Indonesian population but almost equally distributed across rich and poor sub-populations. Given this distribution of hypertension, the 5-6-year life expectancy burden of high blood pressure control is found for men and women across the entire wealth distribution. This finding stands in contrast to many popular understandings of hypertension as a disease of the well off, or a disease of post-nutrition transition populations. However, other researchers have also documented high rates of hypertension among poorer population, arguing that the popular conception of hypertension as a disease of the rich is not

consistent with epidemiological evidence and may lead to suboptimal health policy or resource allocations[39,40].

The key limitation of this study is the use of observational data to estimate the relationship between blood pressure and mortality. For my results to have a causal interpretation, I make the identification assumption that the assignment of blood pressure is random conditional on a set of observed characteristics. If there were unobserved variables that resulted in residual confounding, my estimate would be a biased estimate of the true burden of blood pressure control. However, based on the results of a simulation-based sensitivity analysis, I find that even under high levels of unobserved residual confounding, the size of the gain in adult life expectancy from improving blood pressure control remains large. While the results of these simulations do not solve the identification problem, they suggest that bias from unobserved variables is unlikely to affect the policy conclusions drawn from my results. Within the IFLS, individuals only have blood pressure measurement from one point in time prior to their mortality follow-up. This misses the changes in blood pressure that occur prior to follow-up wave, introducing measurement error into the estimate of blood pressure. However, this type of measurement error would result in a downward bias in the estimate, making my conclusions conservative. While the use of nationally representative data alleviates many issues of selection bias, the final analytic sample is smaller than the overall IFLS sample due to missing data for some individuals. This may result in some degree of selection. Indeed, I find that the life expectancy of the analytic subsample is higher than that over the overall sample, suggesting the analytic sample may be positively selected on health.

Despite these limitations, this study has a number of important strengths. The IFLS is one of the only sources of large nationally representative data with measured blood pressure and reliable mortality follow-up in an LMIC. Empirically, this study is one of the first to estimate the population-level mortality impact of improving blood pressure control using direct population-representative

data. I also move beyond idealized scenarios to estimate the gains across a wide range of plausible policy-relevant scenarios. Similarly, I estimate the gains for the overall population and across wealth quintiles to investigate whether the benefits of hypertension are disproportionately higher for wealthy individuals. Finally, I explicitly confront the potential biases in my observational estimates by showing that the conclusions drawn here are robust to a substantial level of unmeasured confounding.

The results of this study promote hypertension prevention and control as a promising strategy for improving mortality at the population level; however, further research is needed to realize this potential. First, research is needed to establish the cost-effectiveness of various hypertension prevention and treatment strategies to identify which policy options provide the highest rates of return. Next, implementation research is needed to identify the best ways to introduce and scale up hypertension interventions at the population level. Finally, behavioral research is needed to promote health-seeking behavior, preventative health behaviors, and treatment compliance among individuals.

Within Indonesia, improving blood pressure control has the potential to greatly reduce mortality at the population level. While the results presented here are for Indonesia, high-levels of uncontrolled hypertension are not unique to Indonesia. My results suggest that across LMICs, improving blood pressure control can result in large longevity gains. In contrast to many other chronic health conditions, interventions to control blood pressure are also comparatively straight forward and treatments relatively affordable. Therefore, improving blood pressure control has the potential to also be a cost-effective and achievable way of improving longevity in Indonesia and other LMICs.

References

1.   United Nations. Sustainable Development Goals.

2.   Lozano R, Wang H, Foreman KJ, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. *Lancet.* 2011;378(9797):1139-1165.

3.   Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation.* 1998;97(6):596-601.

4.   Preston SH, Stokes A. Sources of population aging in more and less developed countries. *Popul Dev Rev.* 2012;38(2):221-236.

5.   United Nations, Department of Economic and Social Affairs PD. World Population Prospects: The 2017 Revision. 2017.

6.   Lu J, Lu Y, Wang X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet.* 2017.

7.   Lloyd-Sherlock P, Beard J, Minicuci N, Ebrahim S, Chatterji S. Hypertension among older adults in low-and middle-income countries: prevalence, awareness and control. *Int J Epidemiol.* 2014;43(1):116-128.

8.   Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-1913.

9.   Law M, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *Bmj.* 2009;338:b1665.

10.   Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of

hypertension in rural and urban communities in high-, middle-, and low-income countries. *Jama*. 2013;310(9):959-968.

11.   Kalkonde Y V, Deshmukh MD, Sahane V, et al. Stroke is the leading cause of death in rural Gadchiroli, India. *Stroke*. 2015;46(7):1764-1768.

12.   Msyamboza KP, Kathyola D, Dzowela T, Bowie C. The burden of hypertension and its risk factors in Malawi: nationwide population-based STEPS survey. *Int Health*. 2012;4(4):246-252.

13.   Hussain MA, Al Mamun A, Reid C, Huxley RR. Prevalence, Awareness, Treatment and Control of Hypertension in Indonesian Adults Aged 40 Years: Findings from the Indonesia Family Life Survey (IFLS). *PLoS One*. 2016;11(8):e0160922.

14.   Kontis V, Mathers CD, Bonita R, et al. Regional contributions of six preventable risk factors to achieving the 25 × 25 non-communicable disease mortality reduction target: A modelling study. *Lancet Glob Heal*. 2015;3(12):e746-e757. doi:10.1016/S2214-109X(15)00179-5.

15.   Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990--2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2013;380(9859):2224-2260.

16.   Hernan MA, Robins JM. *Causal Inference*. Boca Raton: Chapman & Hall/CRC; 2018.

17.   VanderWeele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology*. 2011;22(1):42-52.

18.   Carretero OA, Oparil S. Essential hypertension part I: definition and etiology. *Circulation*. 2000;101(3):329-335.

19.   Carroll D, Smith GD, Shipley MJ, Steptoe A, Brunner EJ, Marmot MG. Blood pressure reactions to acute psychological stress and future blood pressure status: a 10-year follow-up of men in the Whitehall II study. *Psychosom Med*. 2001;63(5):737-743.

20. Carroll D, Ring C, Hunt K, Ford G, Macintyre S. Blood pressure reactions to stress and the prediction of future blood pressure: effects of sex, age, and socioeconomic position. *Psychosom Med.* 2003;65(6):1058-1064.

21. Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. *Circulation.* 1997;96(1):308-315.

22. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet.* 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8.

23. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol.* 2017.

24. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;2015(373):2103-2116.

25. Cooper RS, Rotimi CN, Kaufman JS, Muna WFT, Mensah GA. Hypertension treatment and control in sub-Saharan Africa: the epidemiological basis for policy. *BMJ Br Med J.* 1998;316(7131):614.

26. Heiniger S, Viswanathan B, Gedeon J, Paccaud F, Bovet P. Trends in prevalence, awareness, treatment and control of high blood pressure in the Seychelles between 1989 and 2013. *J Hypertens.* 2017;35(7):1465-1473.

27. Berry KM, Parker W, Mchiza ZJ, et al. Quantifying unmet need for hypertension care in South Africa through a care cascade: evidence from the SANHANES, 2011-2012. *BMJ Glob Heal.* 2017;2(3):e000348.

28. Witoelar F, Strauss J, Sikoki B. Socioeconomic success and health in later life: Evidence from the Indonesia Family Life Survey. 2009.

29. Kontis V, Mathers CD, Rehm J, et al. Contribution of six risk factors to achieving the 25×25

non-communicable disease mortality reduction target: A modelling study. *Lancet*. 2014;384(9941):427-437. doi:10.1016/S0140-6736(14)60616-4.

30. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Lippincott Williams & Wilkins; 2008.

31. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. *Heart*. 1999;81(4):380-386.

32. Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. Cardiovascular risk factor trends and potential for reducing coronary heart disease mortality in the United States of America. *Bull World Health Organ*. 2010;88(2):120-130.

33. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Math Model*. 1986;7(9-12):1393-1512.

34. Strauss J, Witoelar F, Sikoki B, Wattie AM. The fourth wave of the Indonesian Family Life Survey (IFLS4): overview and field report. *RAND, April*. 2009.

35. Strauss J, Witoelar F, Sikoki B. The Fifth Wave of the Indonesia Family Life Survey (IFLS5): Overview and Field Report. *Calif RAND*. 2016.

36. Chobanian A V, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama*. 2003;289(19):2560-2571.

37. Cutler D, Deaton A, Lleras-Muney A. The determinants of mortality. *J Econ Perspect*. 2006;20(3):97-120.

38. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128. doi:10.1016/S0140-6736(12)61728-0.

39.   Lloyd-Sherlock P, Ebrahim S, Grosskurth H. Is hypertension the new HIV epidemic? 2014.

40.   Lloyd-Sherlock P, Minicuci N, Corso B, Beard J, Chatterji S, Ebrahim S. Diseases of the Rich? The Social Patterning of Hypertension in Six Low-and Middle-Income Countries. *Eur J Dev Res*. 2017;29(4):827-842.

41.   Carretero OA, Oparil S. Essential hypertension. *Circulation*. 2000;101(3):329-335.

Table 1: Descriptive characteristics of the sample in the baseline wave. Adults ages 40+, Indonesian Family Life Survey, 2007, N = 10,085.

	No. or mean	% or SD
Age	53.6	10.8
Female	5298	52.5
Urban Residence	5076	50.3
Province		
North Sumatra	583	5.8
West Sumatra	491	4.9
South Sumatra	428	4.2
Lampung	406	4.0
Jakarta	644	6.4
West Java	1462	14.5
Central Java	1431	14.2
Yogyakarta	698	6.9
East Java	1645	16.3
Banten	248	2.5
Bali	538	5.3
West Nusa Tenggara	628	6.2
South Kalimantan	435	4.3
South Sulawesi	448	4.4
Current marital status		
Never married	149	1.5
Was married	1842	18.3
Currently married	8094	80.3
Completed schooling		
No schooling	1984	19.7
Some schooling	3246	32.2
Primary or more	4855	48.1
Religion		
Islam	8938	88.6
Hindu	495	4.9
Protestant	406	4.0
Other	246	2.4
Primary job		
Retail	1838	18.2

Housework only	1685	16.7
Retired	647	6.4
Agriculture	3125	31.0
Manufacturing	673	6.7
Service	1415	14.0
Not working	176	1.7
Other	526	5.2
Body mass index	23.0	4.2
Number of days of moderate or vigorous physical activity	4.3	2.9

Notes: Body mass index is calculated as measured weight in kilograms over height in meters squared; primary school or more is classified as seven or more years of schooling; analytical models additionally adjust for wealth quintiles but that is not shown since the index was constructed to have 20% of individuals in each quintile.

Figure 1: Continuum of hypertension care in Indonesia. Adults ages 40+, Indonesian Family Life Survey, 2007, N = 10,085. All hypertensive includes individuals who have a systolic blood pressure above 140 mmHg, a diastolic blood pressure above 90 mmHg, or report taking medication for high blood pressure. Estimates were weighted to be sub-nationally representative.
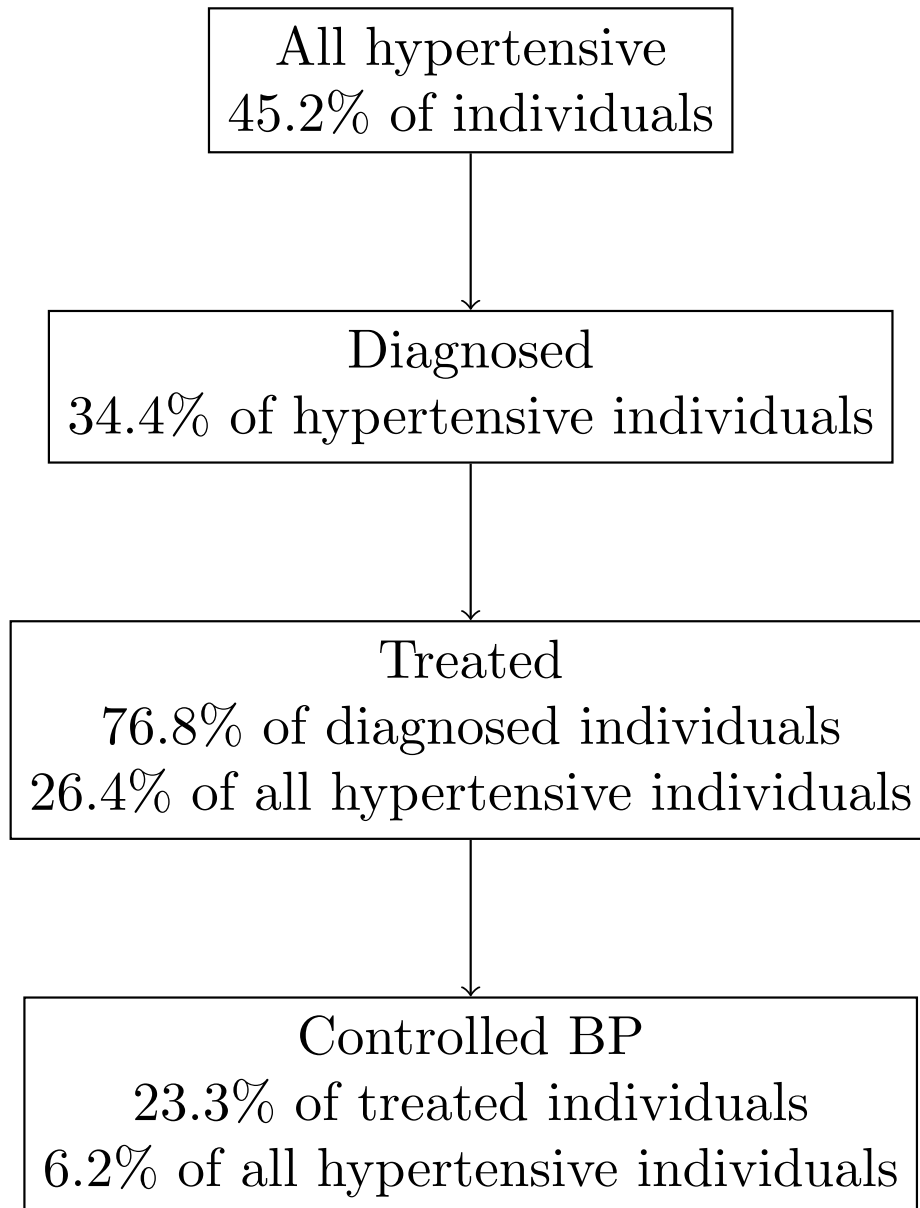
Figure 2: Age-specific prevalence of hypertension in Indonesia. Adults ages 40+, Indonesian Family Life Survey, 2007, N = 10,085 (4,787 Men and 5,298 Women). Error bars represent 95% confidence intervals. Individuals were classified as hypertensive based on measured blood pressure only. Estimates were weighted to be sub-nationally representative.
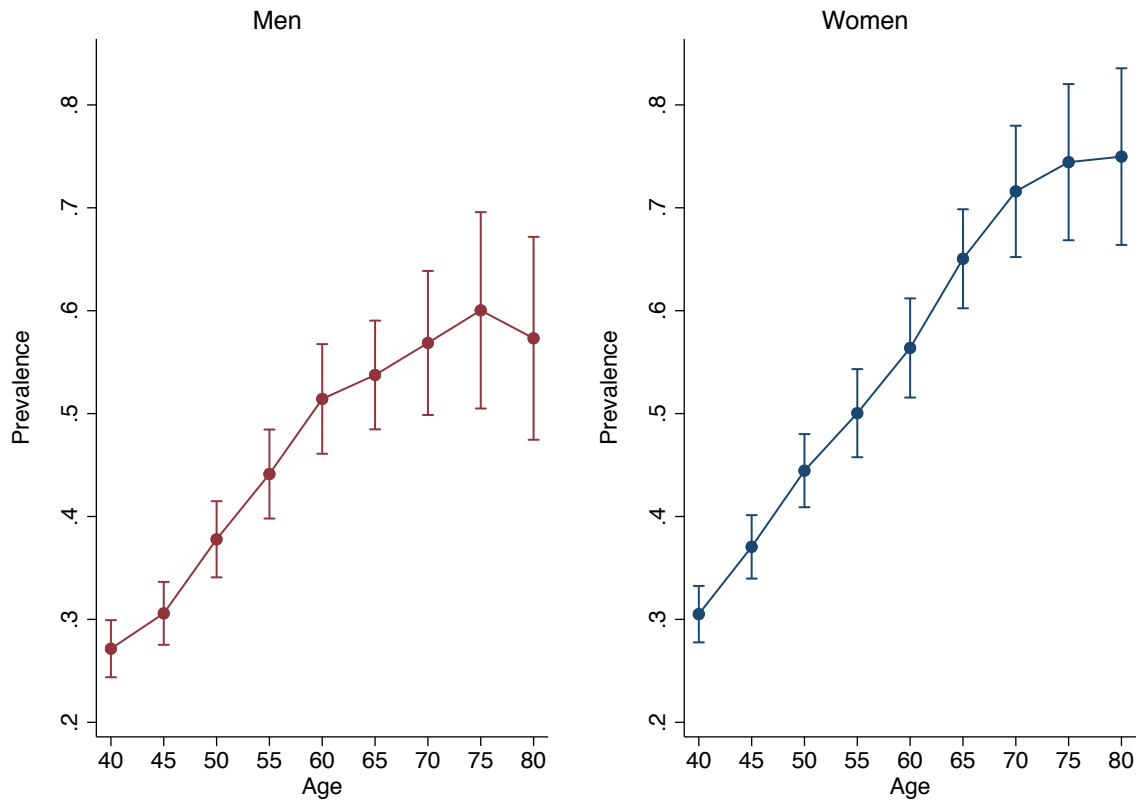
Table 2: Estimated individual-level relationships between blood pressure and mortality. Adults ages 40+, Indonesian Family Life Survey, 2007-2014.

	Men			Women		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Panel A						
Hypertensive	2.0	1.9	1.9	1.6	1.6	1.6
95% CI	(1.6 - 2.3)	(1.6 - 2.3)	(1.6 - 2.3)	(1.3 - 2.0)	(1.3 - 2.0)	(1.3 - 2.0)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Panel B						
Systolic Blood Pressure (10 mmHg units)	1.18	1.17	1.17	1.14	1.14	1.14
95% CI	(1.14 - 1.22)	(1.13 - 1.22)	(1.13 - 1.22)	(1.10 - 1.18)	(1.10 - 1.18)	(1.10 - 1.18)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Person-Age Observations	35,468	35,468	35,468	39,712	39,712	39,712

Estimates are presented as hazard ratios from a Poisson regression of mortality using person-age level data with an offset for time lived within each age. Each estimate corresponds to a different regression (panels A and B use different specifications of the main exposure). Individuals were classified as hypertensive based on measured blood pressure only. Systolic blood pressure was rescaled to 10 mmHg units for interpretability.

Model 1 covariates: age (continuous)

Model 2 covariates: Model 1 + job (cat) + religion (cat) + schooling (cat) + wealth (cat) + urban (cat) + marital status (cat) + BMI (continuous) + days physical activity per week (continuous)

Model 3 covariates: Model 2 + province fixed effects

Table 3: Estimated gain in life expectancy at age 40 under ideal blood pressure control. Adults ages 40+, Indonesian Family Life Survey, 2007-2014/15. N=10,085, PY Obs = 75,280.

	e_{40} Observed	e_{40} Counterfactual	Difference	Difference p-value
Men	34.7	40.0	5.3	<0.001
	(33.8 - 35.6)	(37.5 - 42.5)	(3.2 - 7.4)	
Women	37.6	43.7	6.0	<0.001
	(36.5 - 38.8)	(40.6 – 46.7)	(3.6 – 8.4)	

Notes: Values represent life expectancy at age 40 with 95% confidence intervals in parentheses. Life expectancies were estimated using period life tables. Confidence intervals and p-values were estimated with a bootstrap procedure with 200 replications. Ideal blood pressure control is defined as moving all individuals with a systolic blood pressure > 125 mmHg to 125 mmHg.

Figure 3: Estimated gains in life expectancy at age 40 by size of systolic blood pressure reduction and share of hypertensive individuals that reduce their blood pressure. Adults ages 40+, Indonesian Family Life Survey, 2007-2014/15. N=10,085 (4,787 Men and 5,298 Women), PY Obs = 75,280.
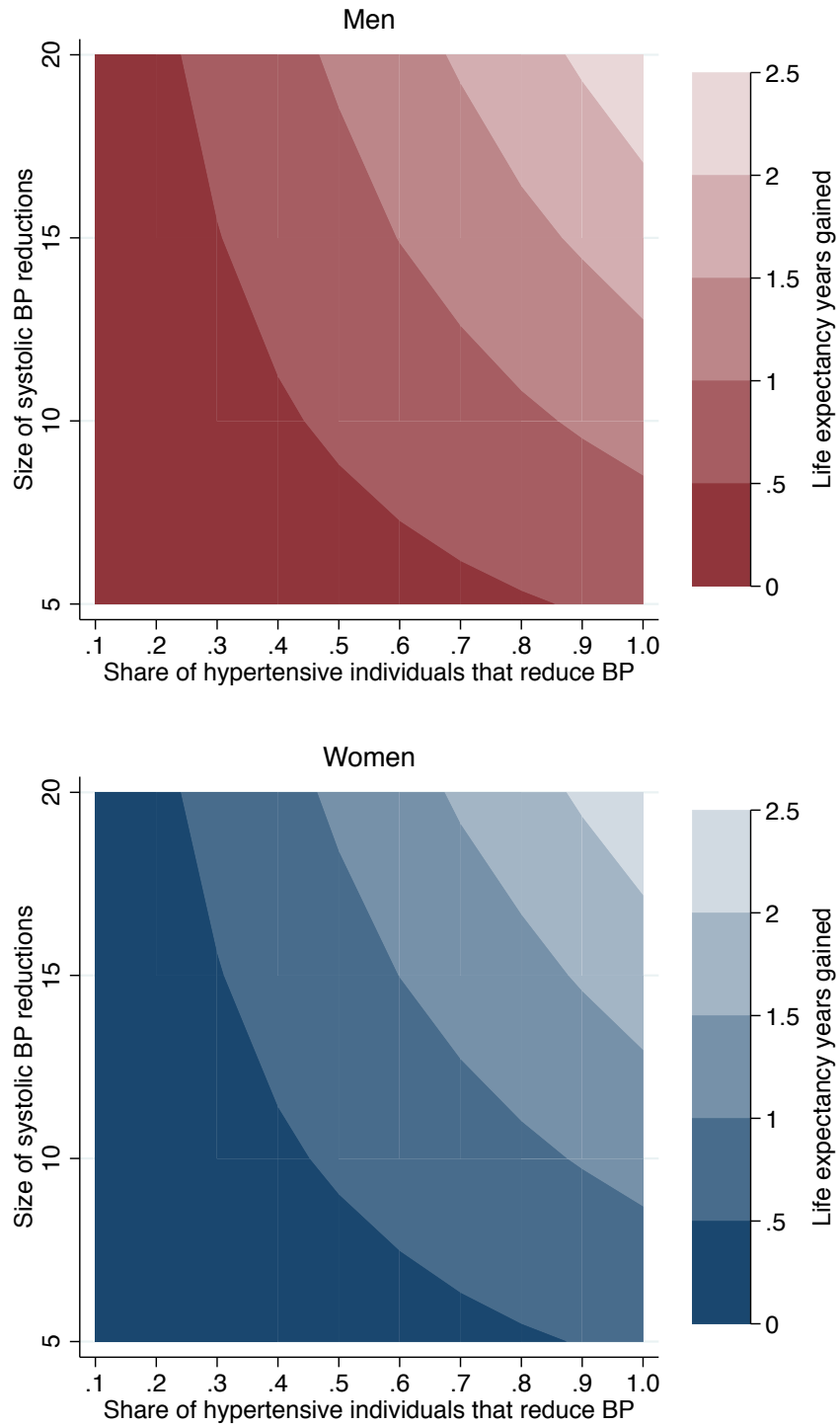
Figure 4: Age-standardized prevalence of hypertension across wealth quintiles separately by sex. Adults ages 40+, Indonesian Family Life Survey, 2007, (4,787 Men and 5,298 Women). Error bars are 95% confidence intervals. The overall population age-distribution was used as the standard. Individuals were classified as hypertensive based on measured blood pressure only. All the estimates were weighted to be sub-nationally representative.
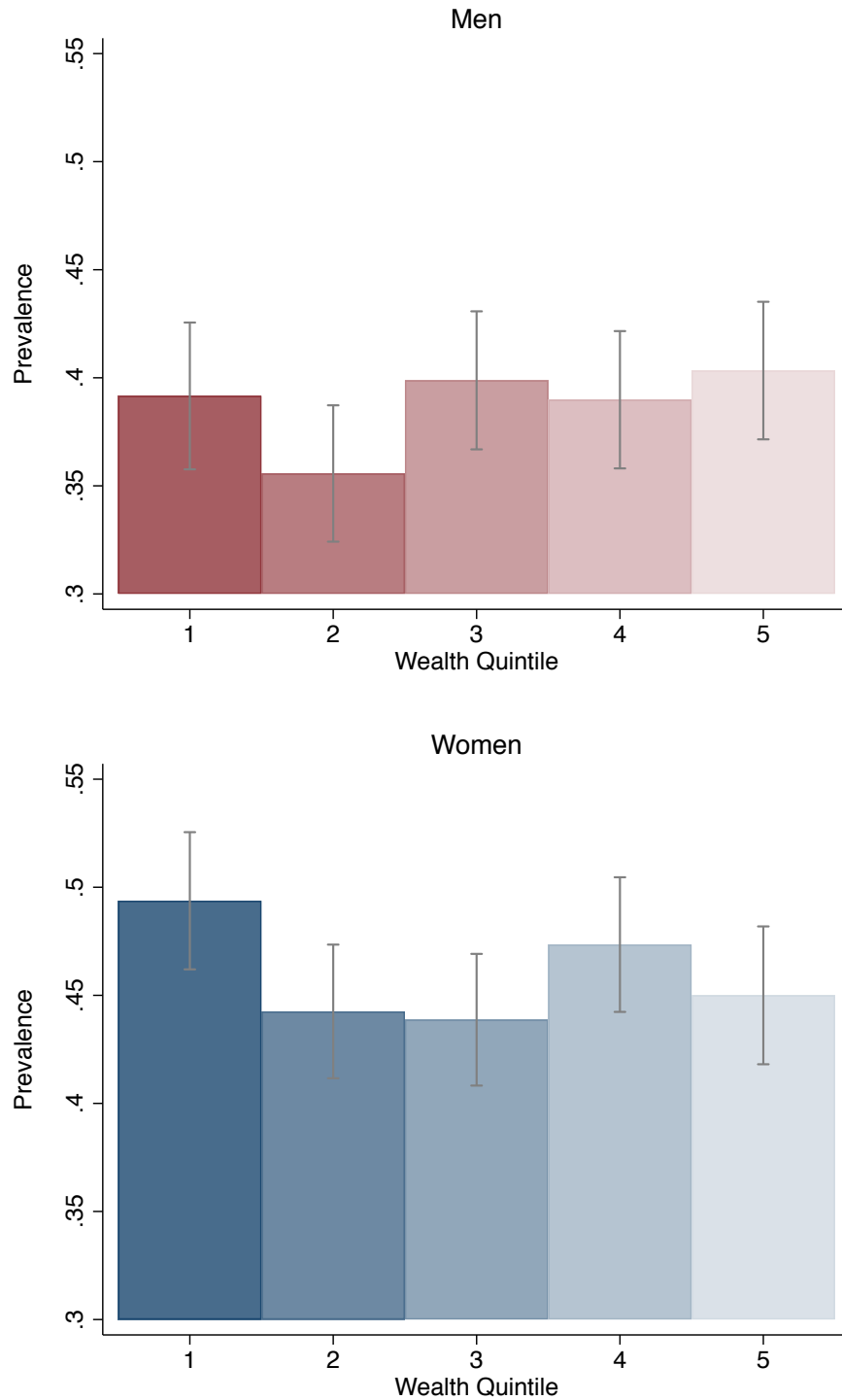
Figure 5: Estimated gain in life expectancy at age 40 after fully controlling blood pressure by wealth quintiles. Adults ages 40+, Indonesian Family Life Survey, 2007-2014/15. N=10,085 (4,787 Men and 5,298 Women), PY Obs = 75,280. Error bars represent 95% confidence intervals.
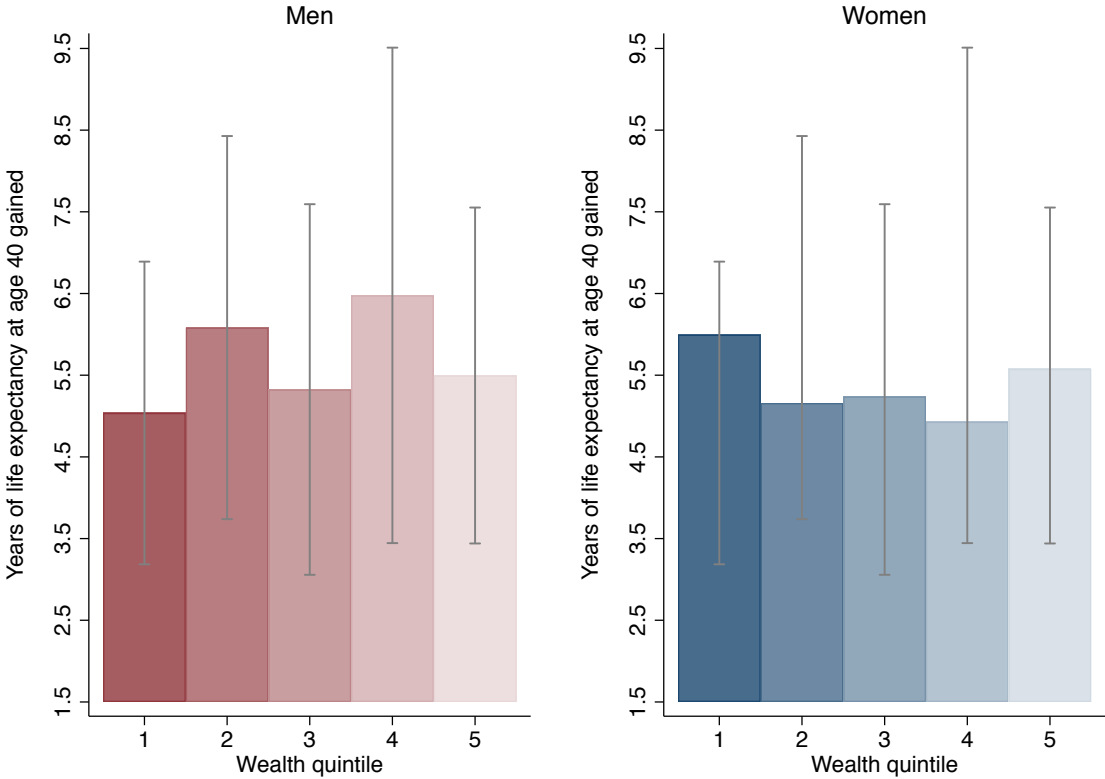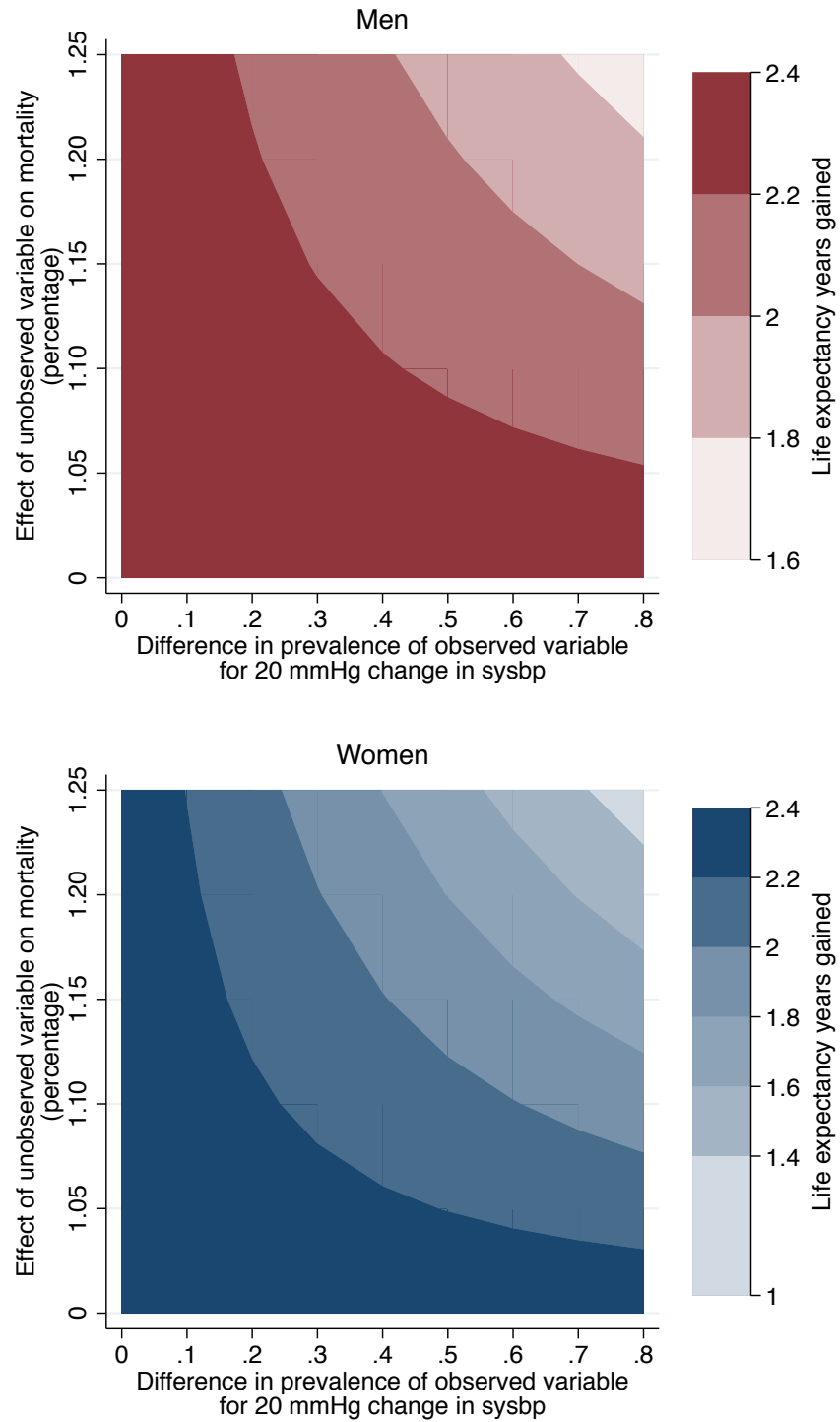
Figure 6: Bias analysis of life expectancy gains from a 20-mmHg systolic blood pressure reduction. Adults ages 40+, Indonesian Family Life Survey, 2007-2014/2015. N=10,085 (4,787 Men and 5,298 Women), PY Obs = 75,280.

Appendix Table 1: Age and death distribution of the sample. Adults ages 40+, Indonesian Family Life Survey, 2007-2014/2015.

	Men				Women			
	N	%	Deaths	%	N	%	Deaths	%
Age group								
40-45	1125	23.5	38	5.8	1247	23.5	44	7.7
45-50	999	20.9	51	7.8	1097	20.7	47	8.2
50-55	781	16.3	83	12.7	882	16.7	54	9.4
55-60	606	12.7	74	11.3	618	11.7	59	10.3
60-65	409	8.5	76	11.6	483	9.1	64	11.1
65-70	408	8.5	114	17.5	456	8.6	110	19.1
70-75	228	4.8	96	14.7	246	4.6	70	12.2
75-80	118	2.5	57	8.7	152	2.9	66	11.5
80+	113	2.4	64	9.8	117	2.2	61	10.6
Total	4787	100.0	653	100.0	5298	100.0	575	100.0

Notes: Age group for deaths are presented as the age of the deceased at the time of the survey in 2007. The actual age of death may fall in the adjacent age group.

Appendix Table 2: Relationship between blood pressure and mortality by wealth quintile. Adults age 40+, Indonesian Family Life Survey, 2007-2014/15

	Men		Women	
	Hypertension	Systolic BP	Hypertension	Systolic BP
Hypertension	1.7		1.9	
	(0.011)		(0.007)	
Hypertension x Wealth Quintile 2	1.0		1.0	
	(0.884)		(0.893)	
Hypertension x Wealth Quintile 3	1.1		0.8	
	(0.710)		(0.514)	
Hypertension x Wealth Quintile 4	1.1		0.6	
	(0.812)		(0.070)	
Hypertension x Wealth Quintile 5	1.1		0.9	
	(0.683)		(0.654)	
Systolic BP		1.10		1.14
		(0.009)		(0.001)
Systolic BP x Wealth Quintile 2		1.06		0.99
		(0.284)		(0.846)
Systolic BP x Wealth Quintile 3		1.02		1.01
		(0.659)		(0.819)
Systolic BP x Wealth Quintile 4		1.08		0.97
		(0.125)		(0.506)
Systolic BP x Wealth Quintile 5		1.12		0.99
		(0.068)		(0.933)
Person-Age Observations	35,481	35,481	39,728	39,728

Estimates are presented as hazard ratios (p-value) from a Poisson regression of mortality using person-age level data with an offset for time lived within each age. Individuals were classified as hypertensive based on measured blood pressure only. Systolic blood pressure was rescaled to 10 mmHg units for interpretability.