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Essays in 'global' health utilization: How distance, gender, and stigma condition whether and when we seek care

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My mother is Amelia Navarrete Bolivar and my father Jorge Fiestas Urbina. They immigrated from Perú to Canada when I was fifteen and raised me through adulthood with great sacrifice. Although each of them loved their profession, they paused their dreams to make space for mine. My mother, who had built a career at the Lima Stock Exchange, cleaned hotels, while my father, a geophysics professor, retired his suit for a factory job. I know they grieved the loss of their former lives, yet my parents started from scratch in a country where they could not roll their 'r'. They did it for me, with love. I learned English, went to university, became Canadian and learned about the values of a country that offers universal health care with equal parts awe and pride. Years later, when I put on a suit and head to do the work I love, I think of my father's steel-toe boots and I think of my mother's cleaning shift. Even though these are now figments of our past – rites of passage to enter our Canadian tribe – their hard work in those hard years gives permanence to the narrative of who I am and will become.

“Sube a nacer conmigo, hermano.
Dame la mano desde la profunda
zona de tu dolor diseminado.
No volverás del fondo de las rocas.
No volverás del tiempo subterráneo.
No volverá tu voz endurecida.
No volverán tus ojos taladrados.
Mírame desde el fondo de la tierra,
labrador, tejedor, pastor callado,
domador de guanacos tutelares,
albañil del andamio desafiado,
aguador de las lágrimas andinas,
joyero de los dedos machacados,
agricultor temblando en la semilla,
alfarero en tu greda derramado,
traed a la copa de esta nueva vida
vuestros viejos dolores enterrados.”

(“Canto General”, Pablo Neruda, 1950)

Essays in ‘global’ health utilization: How distance, gender, and stigma condition whether and when we seek care

Lucia Fiestas Navarrete

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Table of contents

Introduction

The justification of public health systems is grounded on the provision of unimpeded access to medically necessary health care. In turn, use of health services stands at the end of a care-seeking process of varying length, signaling the ability of individuals to seek and obtain the care they need when needed. Ideally, the more urgent, worrying, or evident a symptom is perceived or anticipated to be, the faster the pursuit of medical assistance, whether curative or preventive. Yet, a diversity of contextual and psychosocial factors well beyond what can be explained by need tend to influence whether, when and how care is sought. Giving that utilization constitutes the iceberg tip of an extended, though often unobserved, decision-making process, its study is critical to identify population groups who underuse life-saving health services and understand the hurdles that inhibit their path towards care. Indeed, while underuse of services may result from affordability, distance, culture, stigma, and social status, the equifinality of these barriers is clear – failure to access needed care leads to considerable avoidable morbidity and mortality. Moreover, wherever health systems forgo the opportunity to provide timely primary care, underutilization often leads to a misallocation of resources.

The landscape of health service use varies across, and even within, countries and health sectors irrespective of payment model or health system, yet the fundamental purpose motivating its study is aimed at overcoming the challenges that prevent better and equitable uptake of effective interventions. This dissertation is fuelled by such purpose. Although each chapter poses a specific utilization question relevant to a unique target population, in its entirety, this work seeks to answer the following cross-cutting questions: (i) what are the factors that encourage and challenge utilization of health services, (ii) under which moderating conditions and through which channels is improved utilization supported, and (iii) how can a better understanding of the antecedents of improved utilization contribute to the design of well-targeted health interventions.

In Chapter One, we show that participation in health insurance increases the probability of meeting medical needs while decreasing the probability of incurring catastrophic out-of-pocket health payments in Ghana. By stratifying population subgroups based on travel time to the nearest hospital, we reveal significant effect differences across socio-economic subgroups and find evidence that the poorest benefit most from health insurance – though these benefits are significantly curtailed among geographically remote vulnerable groups. We consistently find that poorer beneficiaries living outside a one-hour travel time to the nearest hospital benefit significantly less from the financially protective effect of health insurance. The fact that higher travel times are associated with utilization and financial protection penalties among vulnerable beneficiaries reveals an insightful decision-making mechanism. Poorer, less educated, and precariously employed geographically remote households tend to forgo care, despite being insured, due to the time, difficulty and/or costs associated with reaching a health facility. For households faced by the disincentive of living far from a hospital, being enrolled in insurance is not a sufficiently effective incentive to utilize services even with the expectation of free care upon arrival.

To ensure that the benefits of health insurance be experienced equitably across socio-geographic groups, policies should be enhanced with parallel improvements in transport infrastructure and focused expansion of the current hospital network to poorly serviced geographic areas. Our findings suggest that travel time is at least one of the decision-making components compelling insured individuals to seek or forgo needed healthcare. Indeed, we show that being enrolled in the health insurance may still not be sufficient to ensure financial risk protection and access to health services among the most disenfranchised socio-geographic subgroups. We highlight that insurance schemes are unlikely to safeguard financial protection from catastrophic expenditure if higher-level healthcare facilities are not geographically accessible. Thus, in an effort to identify the conditions under which health insurance improves utilization to vulnerable beneficiaries, our study offers a novel contribution to the literature from a policy point of view. By targeting the junction of social, economic, and geographic vulnerability, policymakers may be better able to identify a burdened high-risk group that is not yet benefitting from health insurance equitably despite the presence of well-intentioned exemptions. We reveal the extent to which the causal effect of health insurance on utilization derives from geographic accessibility to essential health facilities and highlight the socio-economic groups for whom distance to care matters most.

Drawing on nationally representative survey data from India, Chapter Two offers causal insight into the effect of female empowerment, in the form of marital age, on women's utilization of cervical and breast screening. Our findings suggest that losses in female empowerment attributed to early marriage partly explain Indian women's low cervical and breast screening participation. Indeed, the effect that a one year-increase in marital age exerts on cervical screening is sizeable and commensurable to being enrolled in health insurance. While inadequate insurance coverage constitutes a well-known material challenge to health utilization, we show that losses in agency attributed to young marital age constitute a barrier of like magnitude to women's use of screening services. Moreover, through a structural process analysis, we show that female empowerment does not operate in a vacuum but requires the facilitating condition of an optimal health facility supply environment to promote screening participation. We, thus, reveal the effect of socio-cultural practices exacerbating female disempowerment on women's health utilization. Indeed, if women's status does actually improve with marriage postponement – as suggested by anthropological evidence – our work advances the literature in finding that raising a woman's status by increasing marital age improves her use of health services, and thus matters for public health.

The consequences of women's social status on health are widely discussed in the literature, yet partly owing to the difficulty in measuring the complex phenomenon of disempowerment, few have offered causal insight into how the conditions of social life affect women's health utilization. By exploiting natural variation in the timing of first menstruation, we use marital age itself as a speculum – a tool for improving observation in the interest of understanding the health-related consequences of an overt form of disempowerment. Owing to the woefully low prevalence of opportunistic screening among women, the most common and fatal sites of

cancer in India are the cervix and the breasts. Our research shows that losses in female empowerment attributed to early marriage partly explain Indian women's low screening participation. The policy conclusions derived from our analysis are clear. Elevating the status of women by implementing the existing legal protections against underaged marriage is critical to improve the use of cervical and breast screening. Interventions aiming to address the uniquely high prevalence of women's cancers in India would be wise to reflect on the health utilization consequences that can be attributed to socio-cultural practices exacerbating female disempowerment. Enforcing legal protections against underaged marriage is an actionable arena where both social and health agendas may converge and flourish in the interest of women – and good public policy.

Aiming to contribute a better understanding of health utilization among hard-to-reach groups, Chapter Three investigates the factors that determine the extent of thought given to screening in a sample of high-risk heavy smokers who attended the first free lung cancer screening program in Italy. We show that individuals with greater life-time smoking exposure, and therefore at higher risk of developing lung cancer, tend to contemplate screening less. Moreover, we find that nearly a fourth of the adverse effect of smoking history on thought given to screening could be mediated through its effect on fear of smoking-related health consequences. Indeed, when the effect is mediated, smokers with higher risk profiles tend to contemplate screening more, suggesting that the mediator plays a significantly protective role. Hence, the underlying protective mediational process revealed herein highlights the importance of targeted health-promoting communication aimed at cultivating interest in screening among high-risk groups. Though admittedly brief, the work outlined in this chapter serves the purpose of motivating the approach used to evaluate the cost-effectiveness of lung cancer screening in Italy, thus leading the development of the final chapter.

Considering the voluntary nature of screening and the challenges of engaging ever-smokers, who often disfavour prevention because of the stigma surrounding lung cancer and the fatalistic beliefs associated with a diagnosis, we determined to take stock of adherence. Indeed, the high-risk population that lung cancer screening programs hope to engage differs from those targeted for other types of screening in one important respect – smokers, who battle a nicotine addiction, often experience blame related to the perceived self-infliction of tobacco-related diseases secondary to life-style choices. Thus, it is reasonable to assume that this population may be difficult to reach, and their interest harder to maintain in recurrent, long-term secondary prevention programs. Yet, the literature is replete with evidence showing the comparative effectiveness of invitation strategies on adherence to screening – a wealth of knowledge eerily silent in modelling studies. We opted to transcend adherence from a model input parameter to an essential design element of the screening intervention scenarios that we envisage for the Italian context. With renewed appreciation for the protagonist role that a parameter as unassuming as adherence could play in optimizing the societal value of screening, we conceived a range of screening scenarios with varying invitation strategies.

Finally, Chapter Four evaluates the cost-effectiveness of a population-based lung cancer screening program targeting high-risk prior and current heavy smokers (≥20 pack-years) aged between 55 and 74 years, in Italy. An important focus of our work is to estimate the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) of four specific LDCT-based screening invitation scenarios compared to standard clinical care. To our knowledge, we are the first to integrate the comparative effectiveness of invitation strategies on adherence to screening in the economic evaluation of screening intervention scenarios. In so doing, we assess the cost-effectiveness of a lung cancer screening program designed with increasing levels of engagement vis-à-vis the eligible population and, thus, a view towards improving screening participation within a hard-to-reach population. We underline that this crucial difference sets us apart from modelling studies published thus far. Others have shown that ICERs tend to be highly sensitive to changes in adherence rates. However, introducing variations in adherence in the later stages of the modelling exercise neglects the fact that improvements can and should be an integral part of the design of mass prevention programs. Our model embeds adherence in the design of the screening intervention, as such, improvements in terms of the eligible population's intended participation across screening scenarios result from improvements in the design of interventions. The crux of the matter is that designing interventions that understand and rise to the challenge of compliance in a hard-to-reach population implies further, non-negligible costs.

Our modelling study for the Italian context reveals that population-based LDCT lung cancer screening is cost-effective for a number of screening invitation scenarios. Moreover, we provide evidence that the comparative effectiveness of different invitation strategies intended to improve engagement with the high-risk population of ever smokers generates sufficient variation in uptake so as to increase the cost-effectiveness of strategies. Our findings offer robust support for policy makers, payers and guideline developers who are faced with the important decision of whether to implement population-based, life-saving, lung cancer screening programs. However, an important practical issue to consider when seeking to implement a population-based lung cancer screening program in Italy regards the spatial availability of equipment and specialized human resources for health across the territory. It is relevant to question how quickly and equitably a population-based LDCT lung cancer screening could become accessible to the eligible high-risk ever-smoker population. Indeed, national statistics indicate a clear north-south uptake gradient, whereby adherence among the southern Italian population lags gravely behind its northern counterpart. Acknowledging the health disparities engendered by this geographical divide may offer avenue and justification for future infrastructural investments – especially those pertaining to medical devices – in order to ensure that this, and other mass screening programs, reach the intended national scale equitably across regions.

In seeking to offer insight into the factors that encourage and challenge utilization, the conditions and channels that sustain it, and the design of programs that may, in turn, be sustained by it, this dissertation positions health utilization at centre stage. While the experiences of health, infirmity, disability, and mortality are common denominating factors of a shared humanity, the chapters herein expose distinctive configurations of the 'global'

challenges faced by many to receive care. Indeed, the 'global' in global health utilization refers to the scope of an 'all-too-common' human struggle to seek, reach, afford and receive care – *not* its location. Thus, throughout these works, I have delved, as deeply as data would allow, into the lives of many. And though my findings owe their stars to the power of numbers, as a storyteller, I often chose to think of one. One family. One smoker. One woman. Not the average one, but *any*one. Standing closer to the subject of research has allowed me to understand where 'global' health utilization stories converge, and where they deviate. There is a plethora of conceptualizations of access, and their use often describes the material characteristics that condition whether, when and how the initial contact with a health system occurs. As such, utilization is rightly perceived as a continuum consequent of access to essential material supplies (*e.g.*, the availability of providers, the conditions of roads). Yet, despite being a quantitative researcher, when I allowed myself the privilege to 'think of one', I learned that part of the barriers to access that a Ghanaian family, an Indian woman, and an Italian smoker encounter in each of their paths to care are ideational.

I was made most aware of this while writing about her. The Indian girl who becomes a wife before a woman, for whom the tallest hurdles to cervical and breast screening are the stigmatizing social norms she has internalized. Once the detrimental effect of early marriage on screening participation was established, deep diving into a wealth of qualitative literature enabled me to investigate how the conditions of social life could proscribe women like her from learning to care for their own bodies. Realizing that the more complex barriers to health utilization in need of disentanglement may belong to the ideational world whilst developing this work, caused me to pivot. It was, thus, natural to approach the topic of lung cancer screening with renewed interest in learning about the cacophony of ideas, feelings and fears that are at play when an Italian heavy smoker contemplates participating in organized screening. And though fear and stigma are not explicit model parameters, our cost-effectiveness study recognizes the need to evaluate invitation scenarios that may make it easier, more acceptable, and less frightening for the Italian heavy smoker to participate in screening. Knowledge of and appreciation for the ideational realm underlying health utilization should enrich our understanding of the tangible hurdles posed by absent material structures. Indeed, neither lens is sufficient, and each is necessary. The Ghanaian family made it clear that, despite *a priori* socio-demographic vulnerabilities, distance is distance and some barriers to health utilization are overwhelmingly structural.

As the main edifice of this thesis, I have applied methods to health utilization questions both analytically and aspirationally. Indeed, the methodological transition from frequentist to Bayesian statistics is not based on fluke or fascination with acrobatics. It should expose instead, a decision to apply a continuum of methods allowing me to unearth the world as it is, as well as model the world as it could be. Capable of revealing the ways in which our health systems often fail those in need, the field of 'global' health utilization can be galvanized to both understand and transcend the limitations posed by our current systems.

Chapter 1

Inequalities in the benefits of national health insurance on financial protection from out-of-pocket payments and access to health services: Cross sectional evidence from Ghana

Abstract

Background
A central pillar of Universal Health Coverage (UHC) is to achieve financial protection from catastrophic health expenditure. There are concerns, however, that national health insurance programmes with premiums may not benefit impoverished groups. In 2003, Ghana became the first sub-Saharan African country to introduce a National Health Insurance Scheme (NHIS) with progressively structured premium charges.

Methods
Here, we test the impact of being insured on utilization and financial risk protection compared to no enrolment, using the 2012-2013 Ghana Living Standards Survey (n=72,372). We use probit models with region fixed-effects to estimate the impact of health insurance on the probability that an individual uses medical care when ill or injured, and the probability that an individual lives in a household that incurs catastrophic out-of-pocket health expenditure. We construct a measure of cluster NHIS insurance prevalence rate and used it as an instrumental variable to approximate an exogenous source of variation in insurance participation. To mitigate possible selection bias due to observable characteristics, we calculate a propensity score matching estimator using NHIS-affiliated individuals as the treatment group.

Results
Consistent with previous studies, we observed that participating in health insurance significantly decreased the probability of unmet medical needs by 15 percentage points (p.p.) and that of incurring catastrophic out-of-pocket health payments by 7 p.p. relative to no enrolment in the NHIS. Households living outside a one-hour radius to the nearest hospital had lower reductions in financial risk from excess out-of-pocked medical spending relative to households living closer (-5 p.p. vs -9 p.p.). We also find evidence that in Ghana, the scheme was highly pro-poor. Once insured, the poorest 40% of households experienced significantly larger improvements in medical utilization (18 p.p. vs. 8 p.p.) and substantively larger reductions in catastrophic out-of-pocket health expenditure (-10 p.p. vs. -6 p.p.) compared to the richest households. However, health insurance did not benefit vulnerable persons equally from financial risk. Once insured, poor, low-educated and self-employed households living far from hospitals had significantly lower reductions in catastrophic out-of-pocket medical spending compared to their counterparts living closer.

Conclusion
Taken together, we show that enrolment in the NHIS is associated with improved financial protection but less so among geographically remote vulnerable groups. Efforts to boost not just insurance uptake but also health service delivery may be needed as a supplement for insurance schemes to accelerate progress towards UHC.

1. Introduction

A strategic global health priority, Universal Health Coverage (UHC), is widely recognized as the means to ensure that individuals do not suffer financial hardship when accessing quality health services (1). One major strategy is to expand health insurance coverage. Previously, studies have found that it can help reduce the incidence of catastrophic health expenditure (2,3) and out-of-pocket (OOP) health payments (4,5), as well as boost utilization of health services (6,7), and population health outcomes (8,9). Yet, there are ongoing concerns that national health insurance programmes with premiums may not benefit high-risk and vulnerable groups, especially those who reside in peripheral and rural areas.

Ghana was the first sub-Saharan African (SSA) country to introduce a National Health Insurance Scheme (NHIS). Previous studies have assessed the catastrophic and impoverishment effects of OOP health payments prior to the introduction of the NHIS in Ghana (10,11). They find that 10.7% of Ghanaian households spent more than 10% of their non-food consumption expenditure on OOP health payments (11). Consistent with the international literature, a study by Fenny et al. (12) using data from three Ghanaian districts showed that insured individuals were more likely to seek care for the treatment of malaria, while a study conducted in the Eastern and Central regions found that insurance reduced OOP payments and protected households against impoverishment (13).

Although there is consensus that health insurance can improve utilization and financial risk protection among the insured, the literature offers conflicting evidence on the protective effect of insurance among high-risk beneficiaries. Based on a large randomized assessment of *Seguro Popular*, the Mexican health insurance program, King et al. (5) found that the poorest beneficiaries of insurance experienced greater reductions in catastrophic health expenditure. In contrast, a study by Lu et al. (14) evaluating the impact of *Mutuelles,* the Rwandan community-based health insurance program, found that the poorest beneficiaries had the lowest rates of utilization and highest rates of catastrophic expenditure. Moreover, a recent study by Grogger et al. (15) found that beneficiaries living in areas with access to single-nucleus health facilities experience significantly lower reductions in catastrophic expenditure compared to rural-dwelling beneficiaries with access to larger facilities. Though Grogger et al.'s findings regard beneficiaries with access to differently staffed facilities, they offer insights into the potentially moderating effect of distance to care on the relationship between health insurance and financial risk protection.

A growing body of work has recognized the effect of distance and travel time to health facilities on utilization. Karra et al. (16) pooled data from 21 LMICs to estimate associations between facility distance, child mortality and utilization. Their findings show that children living within 2, 3 and 5 km of a facility have 8%, 16%, and 25% higher odds of neonatal mortality, respectively, compared to children living within 1 km distance. Masters et al. (17) investigated the effect of travel time on the likelihood of in-facility delivery (IFD) among rural households in Ghana and found that a one-hour increase in travel time reduced the odds of IFD by 24%. While the accruing literature reveals important associations between travel time and utilization, there is a lacuna of studies investigating the potentially moderating role

of travel time in the relationship between insurance, utilization and catastrophic expenditure. Moreover, considering the large heterogeneity of populations with limited access to healthcare facilities, a limitation of prior work is an inability to disaggregate findings by social position and test the hypothesis of differential benefit among geographically remote disenfranchised groups.

To address these gaps, we draw on the 2012-2013 Ghana Living Standards Survey data (n=72,371) and examine the impact of the first NHIS in SSA in its first 10 years of implementation. We stratify population subgroups based on travel time to the nearest hospital and household socio-economic characteristics to evaluate the effect of health insurance on financial risk protection and utilization among high-risk and vulnerable beneficiaries with and without limited geographic accessibility to care. We use probit models with region fixed-effects, which were further tested using propensity score matching (PSM) and instrumental variable (IV) estimation methods to address potential selection bias into insurance. Using this sample, we test the hypothesis that the poorest benefit more from national health insurance schemes, but that this is attenuated for beneficiaries living in remote settings.

1.1. Ghana's National Health Insurance Scheme

Established in 2003, the NHIS sought to eliminate user fees and eradicate the financial barriers created by earlier reforms. In the pre-NHIS policy period, OOP payments contributed 48% of the total health expenditure (18). The current NHIS offers free access to a package of diagnostic, inpatient and outpatient services covering 95% of conditions afflicting Ghanaians (19). The scheme is characterized by a 'mandatory-voluntary' *mode of participation* that effectively creates a three-tier enrolment structure whereby (i) formal workers are automatically covered through deductible social contributions, (ii) informal workers are covered voluntarily through annual premium payments and (iii) vulnerable persons are exempted from paying premiums altogether.

Premiums range from 7.20 to 48 Ghana Cedis (GHS) (USD 1.60-10.60) per adult annually, varying according to region of residence. Vulnerable groups that qualify for exemptions include children under 18, adults over 70, pregnant women, individuals with disabilities and indigents. Every member must pay an initial processing fee towards a membership card (GHS 8, c.a. USD 1.82) and a yearly renewal fee (GHS 5, c.a. USD 1.14). Individuals who are not registered in the NHIS are obliged to make OOP payments every time they access health services, which may result in financial hardship.

Mixed participation generates a differential *basis for benefit entitlement*: contributory for formal workers, discretionary for informal workers and non-contributory for vulnerable persons. Though coverage varies widely as a result, Ghana's scheme-type is not uncommon among low- and middle-income countries (LMICs) experimenting with health financing reforms as part of broader UHC strategies (20).

2. Methods

2.1. Source of Data

We use data from the sixth Ghana Living Standards Survey (GLSS-6). The details have been described elsewhere (21) but briefly, GLSS-6 is a nationwide representative household survey conducted by the Ghana Statistical Service in 2012-2013. A two-stage stratified random sampling framework was employed at both regional and national levels. In the first stage, 1,200 enumeration areas (*i.e.* clusters) were sampled across 10 geographic regions with weighted probabilities proportional to population size. In the second stage, 15 households were randomly selected from each cluster. Thus, covering a nationally representative sample of 72,372 individuals living within 16,772 households across 1,200 clusters. We restricted the study sample to individuals who were either enrolled in the NHIS (treatment group) or did not have any form of insurance (control group).

2.2. Outcome Measures

Catastrophic expenditure is a binary outcome variable indicating whether OOP health payments absorbed an excessive share of household budget. OOP health payments consist of annual household-level spending on both inpatient and outpatient services and all other reported spending directly related to the receipt of health services. We express OOP health payments as a ratio of total household non-food consumption (22), which is obtained by deducting total annual food consumption (F) from each household's total annual real consumption (C_h): $OOP_h/(C_h - F_h)$. Catastrophic expenditure corresponds to OOP health payments that absorb more than 10% of household non-food consumption: $x < OOP_h/(C_h - F_h) < 1$, where $x = 0.1$. Utilization is a binary outcome variable indicating whether an individual used medical services if she were ill or injured in the previous two weeks of the survey. While our utilization outcome variable operates at individual-level, the financial risk protection outcome variable operates at household-level. This reflects the fact that: (i) expenditure is an intra-household, rather than individual, decision, and (ii) GLSS-6 reports expenditure data only at household level.

2.3. Independent variables

We created a binary variable 'NHIS' to represent an individual's participation in the NHIS, where 1= insured and 0, otherwise. The socio-demographic variables contained in the medical utilization analysis include: age and gender of the respondent, gender, education and employment status of the household head, household size, household consumption expenditure and rural residence. We included a binary variable to indicate whether an individual lives in a household with at least one elderly member, as well as a dummy variable indicating whether an individual lives in a household located outside a one-hour travel radius to the nearest hospital. A radio ownership dummy variable was built to detect the effect of public health education, often accessed via radio programming. We used two dummy variables to indicate whether an individual who self-reported illness or injury in the two weeks prior to the survey was forced to stop her usual activities due to the ailment's severity

and whether an individual suffered from any kind of disability. We included ten regional dummy variables to control for heterogeneity of unobserved health systems-related characteristics across regions. Due to the household-level nature of the financial risk protection analysis, we use insured households as the 'NHIS' treatment group, whereby household insurance status derives from that of the household head.

2.4. Statistical models

We use probit models with region fixed-effects to estimate the impact of health insurance on the probability that an individual uses medical care when ill or injured, and the probability that an individual lives in a household that incurs catastrophic OOP health expenditure (Equation 1). Each model postulates that utilization (m_1) and financial risk protection (m_2) are functions of insurance status $c_1 NHIS_i$, in addition to socio-demographic, household and geographic characteristics:

$$Y_{ihr}^{m_{1,2}} = \alpha_1 + c_1 NHIS_i + X_i'\beta_1 + W_{ih}'\delta_1 + Z_{ihr}'\zeta_1 + \varepsilon_{1ihr} \quad (1)$$

where individual-level (i) variables are represented by the vector β, household-level (h) variables by the vector δ and region-level (r) dummy variables by the vector ζ.

2.5. Evaluating potential effect differences

To examine the effect of health insurance on utilization, we restricted our study sample to individuals who reported being sick or injured in the two weeks prior to the survey (n=10,311), while to study financial risk protection, we restricted our sample to individuals whose households made any OOP health payments in the year of the survey (n=25,971). To evaluate differences in the effect of health insurance across vulnerable subgroups, we disaggregated our sample across levels of household socio-economic characteristics. These include household consumption expenditure, education and employment status of the household head. Across each subgroup, we tested whether travel time to care (within *vs.* outside a one-hour radius to the nearest hospital) influences the effect of insurance on utilization and financial risk protection.

We use travel time to care since it implicitly encompasses not only distance but also difficulty of travel and may better reflect the decision-making process to utilize services (17). We select hospitals as the single site from which to derive travel time because they tend to offer a comprehensive array of services available through the NHIS (*e.g.* diagnostic, inpatient and outpatient). The median time travelled to the nearest hospital in our sample is 60 minutes (IQR: 60) and the mean 73 (SD: 69.4). Hence, we proceed with a median-split to categorize subpopulations within and outside a one-hour travel time. Aligned with the relevant literature, previous studies based in SSA countries confirm that travel times to health facilities of at least one hour present a sufficient barrier to access services (17,23).

2.6. Identification strategy

A key methodological challenge facing our study is the requirement that the individual decision to enrol in health insurance be uncorrelated with observable and unobservable determinants of utilization and health expenditure. This assumption is challenging, as insurance status is likely to incorporate an *ex-ante* need for medical care, with the consequent problem of selection bias. The importance of testing and accounting for potential endogeneity of insurance participation in models explaining variability in health service use and catastrophic expenditure has been investigated widely (24,25).

Drawing from the approach used by Lu et al. (14), we constructed a measure of cluster NHIS insurance prevalence rate and used it as an IV to approximate an exogenous source of variation in insurance participation. Our data is composed of 1,200 clusters, each representing a demarcated geographic area that consists of 15 households. The NHIS prevalence rate for an individual i living in cluster k equals the number of insured persons in cluster k minus the insurance status of the same individual divided by the total number of persons in the cluster. The assumptions that individuals living in geographic clusters characterized by high insurance rates are more likely to be insured (relevance) and that cluster insurance rate affects neither an individual's decision to use medical services nor a household's decision to spend on health directly (exclusion) are reasonable and discussed in Lu et al. (14).

We postulate that a correlation between the endogenous regressor and our instrument is possible for different reasons. For example: (i) clusters of enrolled individuals might arise because residents in some geographical areas share higher quality of medical services, and (ii) individuals living in a geographic area with a higher concentration of insured individuals may be influenced by the enrolment behaviour of their peers (26). The peer-effect claim is supported by a recent study, which revealed that presenting health insurance information to informal groups had a larger effect on retention and trust in the insurance scheme than full premium subsidies (27).

We included cluster insurance rate in first-stage probit regressions and obtained the predicted probabilities of NHIS participation for each individual:

$$NHIS_i = \alpha_2 + c_2 cluster\ rate_i + X_i'\beta_2 + W_{ih}'\delta_2 + Z_{ihr}'\zeta_2 + \varepsilon_{2ihr} \qquad (2)$$

which were used to estimate the effect of health insurance on utilization and financial risk protection in the respective second-stage IV regressions:

$$Y_{ihr}^{m_{1,2}} = \alpha_3 + c_3\widehat{NHIS}_i + X_i'\beta_3 + W_{ih}'\delta_3 + Z_{ihr}'\zeta_3 + \varepsilon_{3ihr} \qquad (3)$$

To mitigate possible selection bias due to observable characteristics, a PSM estimator was calculated, using NHIS-affiliated individuals as the treatment group (28). We used the nearest neighbour (NN) matching without replacement approach and restricted matching within a

caliper of 0.0001 to avoid matching by a neighbour very far from the insured individual but with the closest propensity score.

We matched treated and control individuals based on covariates that may influence selection into insurance. For the utilization outcome equation, we matched individuals based on (i) demographic (*i.e.* age, gender), (ii) individual-level medical need (*i.e.* illness severity), (ii) head-of-household (*i.e.* education, employment status), (iii) household (*i.e.* consumption expenditure, size) and (iv) geographic (*i.e.* rural residence and travel time) characteristics. For the catastrophic expenditure outcome equation, we matched individuals based on (i) head-of-household (*i.e.* age, gender, education, employment status), (ii) household (*i.e.* consumption expenditure, size), (iii) household-level medical need (*i.e.* presence of elderly members, disabled members, ill members) and (iv) geographic (*i.e.* rural residence, travel time) characteristics. When conditioning on these covariates, the observed outcomes of uninsured units can be reasonably used to estimate the counterfactual outcome of insured units in the case of no treatment.

Standardized differences and t-tests for the covariates used to satisfy the balancing property offer evidence that the propensity scores were properly identified (Appendix A, Tables A1-2). These tables report, separately for the two outcomes, the mean characteristics by insurance status. Differences between the insured and uninsured groups are arguably small and become even smaller after matching. These are the subsets of treated and control subjects that are effectively used in the estimation of the causal effect of interest throughout the matched probit specifications (without and with IV). Common support for each model can be assessed by examining the distribution of propensity scores across groups (Figures 1-2).

3. Results

Table 1 presents descriptive statistics for insured and uninsured groups in our sample. 36% of individuals were insured by the NHIS. Among the 45,405 uninsured individuals, 16% were insured in the past but had failed to renew their annual NHIS membership, while the remaining 84% had never been insured. The most frequently reported reason for never having registered for health insurance (63%) and for failing to renew the NHIS membership (38%) was having "No money". As it regards enrolment, 67% of insured individuals became NHIS members by paying a premium, while 31% qualified for a premium exemption. Mean premium payment was GHS 7.74. Moreover, within premium exempted groups, insured individuals were a persistent minority: 38% of children under 18, 48% of adults over 70, 46% of pregnant women and 37% of individuals living with disabilities were insured.

Table 2 presents probit regression results generated from the unmatched data, PSM data and PSM data with IV for utilization analyses in the sample of individuals that reported illness or injury two weeks prior to the survey. Results from the first stage IV-probit regression are shown in Column (3), providing strong evidence that cluster insurance rate significantly predicts participation in the NHIS. Findings on the effect of the NHIS on utilization are positive, sizeable and significant across specifications: individuals insured by the NHIS are

more likely to use medical services when needed compared to their uninsured counterparts after controlling for other factors.

Table 3 presents probit regression results for the financial risk protection analyses generated from the unmatched data, PSM data and PSM data with IV. Column (3) shows the results from the first stage IV-probit regression, which instruments health insurance with cluster insurance rate and offers strong evidence that the instrument significantly predicts participation in the NHIS. Findings are consistently negative and significant across specifications: after controlling for covariates, individuals enrolled in the NHIS are significantly less likely to live in households that incur catastrophic health expenditure.

The NHIS coefficient in Tables 2 and 3 remains stable across models, changing slightly with the IV estimation. Since we have no prior regarding the size and direction of coefficient changes when the IV is implemented, these results show that the impact of the NHIS is robust and in the expected direction. The fact that the NHIS coefficient on utilization is smaller in the PSM-IV analysis implicitly confirms that the instrument addresses selection bias into insurance. Assuming that the IV approach overcomes the bias of naïve estimators, we suggest that coefficients associated with the PSM-IV specifications represent the effect that we are actually interested in – that of health insurance on a sample of individuals who comply with the assignment to treatment given by cluster rate. Hence, we use PSM-IV specifications to compute local average treatment effect estimates when disentangling main effects into subgroup estimates.

A common objection to the classic catastrophic expenditure definition employed here is that it ignores important differences in the budget capacity of poor and non-poor households. To test the robustness of our results, we used Wagstaff and Eozenou's (22) unified financial risk protection methodology, yielding unique outcome variables relevant to population groups above and below the poverty line (Appendix B, Figure B1). The comprehensive rationale and implementation of the method can be found in the original article (22). Our results are robust to the use of different outcome variables. Table 4 shows that enrolment in the NHIS significantly reduces financial hardship resulting from OOP health payments among families living above and below the poverty line.

Table 5 presents effect estimates of health insurance on utilization and financial risk protection. Our results show that enrolment in the NHIS increases the probability of meeting medical needs by 15 percentage points (p.p.) while decreasing the probability of incurring catastrophic OOP health payments by 7 p.p. relative to no enrolment. When disaggregating the population based on proximity to care, we observe that the effect of insurance on improved utilization is larger among insured individuals living within a one-hour travel time to the nearest hospital (17 p.p.-increase) than for individuals living farther than one hour away (14 p.p.-increase). We also observe that the effect of health insurance on improved financial risk protection is larger among insured individuals living within a one-hour radius to the nearest hospital (9 p.p.-decrease in catastrophic expenditure) than for insured individuals living farther (5 p.p.-decrease). Overall, the effects of health insurance on improved

utilization and financial risk protection are most pronounced among insured individuals living within one-hour travel time to a hospital.

Table 6 presents effect estimates of health insurance on the probability of utilization across different socio-economic subgroups and disaggregated by proximity to care. Enrolment in the NHIS has a positive, sizable and statistically significant effect on medical service use across socio-economic subgroups relative to no enrolment. The effect of health insurance on improved utilization is significantly larger among the poorest 40% of the population (18 p.p.-increase), compared to the richest 40% (8 p.p.-increase) (p=0.003). When we disaggregate socio-economic groups based on proximity to care, we find that vulnerable groups (*i.e.* individuals living in poorer, lower educated and self-employed households) benefit consistently less from health insurance when living outside a one-hour radius from the nearest hospital.

Table 7 presents the effect estimates of health insurance on the probability of catastrophic OOP health expenditure across socio-economic subgroups and disaggregated by proximity to care. Overall, enrolment in the NHIS has a negative, sizable and statistically significant effect on financial risk due to catastrophic health expenditure across socio-economic subgroups relative to no enrolment. The effect of health insurance on improved financial risk protection is larger among the poorest households (10 p.p.-decrease in catastrophic expenditure), compared to the richest (6 p.p.-decrease) (p<0.10). We observe larger reductions of catastrophic health expenditure among households headed by members with higher compared to lower education (14 p.p. *vs.* 3 p.p.) (p<0.000) and among households headed by employed, compared to self-employed members (16 p.p. *vs.* 6 p.p.) (p=0.04). When we disaggregate socio-economic groups based on proximity to care, we consistently find that vulnerable groups who live farther than one hour away from the nearest hospital benefit significantly less from the financial protection afforded by health insurance.

3.1. Robustness checks

We conducted a series of robustness and sensitivity tests on our PSM models by comparing relative effects across three alternative matching methods. In addition to NN without replacement, we applied kernel, radius and Mahalanobis matching. We verified the covariate balance graphically across matching procedures by comparing the standardized bias in matched and unmatched samples (Appendix C, Figures C1-2). In addition, we used two balancing tests for each alternative method: standardized differences and t-tests (results not shown) and estimated average treatment effects on the treated (ATT) for each outcome variable obtained from the four matching methods. Table 8 shows that the ATT estimates for the two outcomes do not change significantly between matching methods.

We conducted simulation-based sensitivity analyses proposed by Ichino et al. (29), which allowed us to use matching estimators in order to assess whether the estimated ATTs are robust to possible failures of unconfoundedness. The distribution of the binary confounding factor *U* is fully characterized by the choice of four parameters,

$$p_{ij} \equiv \Pr(U = 1 | T = i, Y = j) = \Pr(U = 1 | T = i, Y = j, W) \quad (4)$$

with $i, j \in \{0,1\}$, which give the probability that *U=1* in each of the four groups defined by the treatment status *T* and the outcome value *Y* (29). Given these parameters, we then predict a value of the confounding factor for each treated and control subject and we re-estimate the ATT including the simulated *U* in the set of matching variables *W*. By changing the assumptions about the distribution of *U*, we were able to assess the robustness of the ATT with respect to different hypotheses regarding the confounding factor. The comprehensive rationale and implementation of the method can be found in the original article (29).

Table D1 in Appendix D presents the results from the sensitivity analyses of the propensity score for medical utilization based on the effect of 'calibrated' confounders. Each row of the first four columns contains the four probabilities $p_{ij} \equiv \Pr(U = 1 | T = i, Y = j)$, with $i, j \in \{0, 1\}$, which characterize the binary distribution of the confounding factor, by treatment status and outcome, under which the ATT has been estimated (29). To facilitate a comparison between baseline and simulated results, the first row shows the ATT estimate obtained with no confounder in the matching algorithm. The second row reports the ATT estimated with a neutral confounder. The subsequent rows show how the baseline estimate changes when the binary confounding factor *U* is calibrated to mimic different observable covariates (confounder-like) and is then included in the matching algorithm. The first case sets the distribution of *U* to be similar to the distribution of *female*. In this case, given that 58% of the subjects who are exposed to treatment and use medical care are female, by setting $p_{11} = 0.58$ we impose that the same fraction of subjects be affected by the confounding factor and be assigned a value of *U* equal to 1.

Under a deviation from the CIA with these characteristics, the ATT is estimated to equal 0.15. This estimate only differs from that obtained in the absence of confounding effects in the third decimal digit (by 0.002) and remains statistically significant. The other rows assume that the distribution of *U* is in turn comparable to the distribution of observable variables like: *female household head, self-employed household head, rural residence, elderly household member, hospital outside a one-hour travel time, radio ownership, severity of illness or injury* and *disability*. Only in the case of the confounding factor behaving like an *elderly household member* (associated with an outcome effect of Γ=0.85 and a selection effect of Λ=1.44) does the ATT differ by 0.8 percentage points from the baseline estimate, but it still remains statistically (and economically) significant.

Table D2 in Appendix D presents similar results from the sensitivity analyses of the propensity score for catastrophic OOP expenditure based on the effect of calibrated confounders. The baseline ATT estimate obtained with no confounder in the matching set equals to -0.02. Under a deviation from the CIA with the characteristics of variables like having a *household member with a disability* (Γ=1.95, Λ=1.04) and having a *household member severely sick or injured* (Γ=1.27, Λ=1.09), the ATT is estimated to equal -0.03. In these cases, insurance treatment further decreases catastrophic health expenditure by 0.8 percentage points from the baseline estimate. Taken in conjunction, the simulations convey

robustness of the baseline matching estimate of the ATT of health insurance in Ghana. These simulations also show that both the outcome and the selection effect of *U* must be strong in order to represent a credible threat to the significance of the estimated ATT.

In addition, Ichino et al.'s sensitivity analysis allows us to explore the characteristics of the confounding factor *U* under which the point estimate of the ATT becomes close to zero. This is done in Tables D3-4. In these simulation cases, we explore the characterization of 'killer' confounders by varying the defined outcome and selection effect differences: $d = p_{01} - p_{00}$ and $s = p_{1.} - p_{0.}$, respectively. When imposing values for the parameters p_{ij}, we simulate the confounding factor exclusively associated with the preferred values of *d* and *s,* which we can associate with the parameters Γ and Λ, respectively. These estimated odds ratios provide a measure of the observed effect of the confounder *U* on the outcome (Γ) and on the selection (Λ) into treatment (controlling for *W*).

Table D3 in Appendix D presents the results from the sensitivity analyses of the propensity score for medical utilization based on the effect of 'killer' confounders. Along every row, *d* is kept fixed while *s* is increasing. Along every column, the opposite happens. In each row, the predetermined value of *d* is associated with the range of variation of the estimated outcome effect Γ that characterizes the corresponding simulated confounders. Similarly, in each column, the value of *s* is associated with the range of variation of the selection effect Λ that characterizes the simulated confounders. Hence, moving to the right across each row, the confounding factor has a greater influence on the selection into treatment (keeping the outcome effect fixed). Moving down each column, the confounding factor has a greater influence on the untreated outcome (keeping the selection effect fixed).

The results show that both the outcome and the selection effect need to be very strong in order to 'kill' the ATT. For low values of the outcome effect, such as *d*=0.1 ($\Gamma \in [1.5]$) in the first row, the point estimate obtained when *U* is included in the matching set is never smaller than 0.11, and it does not lose significance even when faced with very high (and fairly implausible) values of the selection effect. A comparison with the results of Table D1 reveals that the cases in which the confounding factor is calibrated to match specific observed characteristics of subjects correspond to cells close to the top left of Table D3, with both *d* and *s* smaller than 0.2. The comparison between both tables suggests that even if the unobserved confounding factor had outcome and selection effects substantially larger than those of the observed covariates, it would not cause much change in the estimated ATT.

Table D4 in Appendix D presents the results from the sensitivity analyses of the propensity score for catastrophic health expenditure based on the effect of 'killer' confounders. For low values of the outcome effect, such as *d*=0.1 ($\Gamma \in [1.5]$) in the first row, the point estimate obtained when *U* is included in the matching set is never smaller than -0.03, and it does not lose significance even when faced with very high values of the selection effect. To summarize, all four sets of sensitivity analyses based on the effect of 'calibrated' and 'killer' confounders for medical utilization and catastrophic health expenditure convey robustness of the matching estimate with respect to reasonable failures of the CIA.

4. Discussion

Detecting the conditions under which national health insurance systems offer protection to the insured and identifying the least protected beneficiaries is an important, albeit largely under-investigated area of research. Our findings show that participation in the NHIS increased the probability of meeting medical needs and decreased the probability of incurring catastrophic OOP health payments relative to no enrolment. We reveal significant effect differences across socio-economic subgroups and find evidence that the poorest benefit most from health insurance, though these benefits are significantly curtailed among geographically remote vulnerable groups.

We consistently find that poorer beneficiaries living outside a one-hour travel time to the nearest hospital benefit significantly less from the financially protective effect of health insurance. The fact that higher travel times are associated with utilization and financial protection penalties among vulnerable beneficiaries reveals an insightful decision-making mechanism. Poorer, less educated and precariously employed geographically remote households tend to forgo care, despite being insured, due to the time, difficulty and/or costs associated with reaching a health facility. For households faced by the disincentive of living far from a hospital, being enrolled in insurance is not a sufficiently effective incentive to utilize services even with the expectation of free care upon arrival.

We show that being enrolled in the NHIS may still not be sufficient to ensure financial risk protection and access to health services among the most disenfranchised socio-geographic subgroups. They highlight that insurance schemes are unlikely to safeguard financial protection from catastrophic expenditure if higher-level healthcare facilities are not geographically accessible. Our findings are in line with a recent analysis of the Community-based Health Planning and Services initiative in Ghana, which underlined the importance of bridging geographical access to healthcare as prerequisite to delivering on the promise of universal coverage (30).

Our findings are consistent with recent work by Grogger et al. (15) who showed that *Seguro Popular* provided greater financial protection in areas proximate to larger health facilities. In addition to confirming these findings, the most novel contribution of our paper is to unveil the differential effects of health insurance by distance to care and socio-economic characteristics. In doing so, we sought to draw more convincing conclusions regarding the benefits of health insurance as experienced by families with distinctive *a priori* degrees of vulnerability. Our results are also aligned with those obtained by previous studies on Ghana (10,11) and elsewhere (31), which voiced the inherent challenge of providing financial protection to the most vulnerable beneficiaries. Taken together, our findings confirm that improving the geographic availability of quality health services is as important as promoting enrolment in national health insurance schemes in order to boost progress towards UHC.

Moreover, the fact that households headed by less educated members benefit less from the financially protective effect of health insurance indicates that navigating and securing the benefits of a national health insurance product is dependent upon the education level of

beneficiaries. This partially reflects Hart's inverse care logic (32), explaining why beneficiaries with low education levels and reasonably poor understanding of health insurance would be less able to leverage insurance claims.

To ensure that the benefits of health insurance be experienced equitably across socio-geographic groups, UHC-driven policies should be enhanced with parallel improvements in transport infrastructure and focused expansion of the current hospital network to poorly serviced geographic areas. Our findings suggest that travel time is at least one of the decision-making components compelling insured individuals to seek or forgo needed healthcare. As such, we recommend the implementation of targeted health education interventions aiming to incentivize prompt care-seeking behaviour among geographically remote vulnerable groups. Our findings also indicate shortcomings concerning the implementation of policies meant to protect vulnerable people. In Ghana, vulnerable groups are exempted from paying enrolment premiums, however, the implementation of these policies is challenging. There may be important underlying conflicts between healthcare providers facing budget constraints and reimbursement uncertainty, and policies seeking to broaden access to care among vulnerable beneficiaries. Thus, implementation inefficiencies may be part of the explanation as to why some of the most vulnerable NHIS enrolees are least protected from financial hardship.

These implications extend well-beyond Ghana, as other SSA countries with similar fiscal constraints are experimenting with hybrid health insurance schemes alike. Among them, Rwanda and Ethiopia have exemptions built-in their health financing structures aiming to target destitute groups. Our findings suggest that, although exemptions are part of the way forward, closer attention should be paid to long-term investments in road quality, supply network expansion and health education policies. Indeed, by targeting the junction of social, economic and geographic vulnerability, policymakers may be better able to identify a burdened high-risk group that is not yet benefitting from health insurance equitably despite the presence of well-intentioned exemptions.

These findings should be viewed in light of the following limitations. First, while the comprehensive objectives that our work seeks to examine include access to promotive, preventive, curative, rehabilitative and palliative health services, we are able to assess the impact of health insurance on medical utilization focusing on curative care only. Second, though we consider UHC not as an end in and of itself but the means towards better health outcomes, our study assesses the effect of health insurance on improved health service use. While there is reason to believe that access to care leads to improved health outcomes, we do not directly measure the effect of the NHIS on these outcomes. Third, due to data availability our study measures utilization two weeks prior to the survey and as such, offers a partial picture of utilization and a lower bound estimate of annual health service use. Fourth, the cross-sectional nature of our data has allowed us to capture annual OOP health expenditure at the time of the survey, which we have found to be sufficient to affect household financial wellbeing. However, it is possible that households incur recurrent catastrophic health expenditures, whose consequences may be more detrimental, and for which longitudinal data is needed.

Overall, this study supports the UHC objective of the Ghanaian NHIS and offers valuable lessons to other low- and middle-income countries seeking to broaden access to quality healthcare while lessening reliance on OOP payments. To our knowledge, our study is the first to investigate the effect of health insurance on utilization and financial risk protection across socio-economic characteristics based on travel time to care. Our findings point to the need for developing more effective approaches to include vulnerable socio-geographic groups in nascent national health insurance systems and to ensure that they benefit equitably from utilization and financial protection. Finally, in an effort to identify the conditions under which health insurance offers protection to vulnerable beneficiaries, our study offers a novel contribution to the literature from a policy point of view. We reveal the extent to which the social benefit of health insurance derives from geographic accessibility to essential health facilities and highlight the socio-economic groups for whom distance to care matters most.

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Table 1. Descriptive statistics, Ghana 2012-2013

	Uninsured		NHIS Insured	
	N	(%)	N	(%)
Individuals	45,405	(63.68)	25,894	(36.32)
Households	11,292	(67.44)	5,452	(32.56)
Age categories				
Under 5	5,844	(12.87)	3,584	(13.84)
5 to 18	16,057	(35.36)	9,659	(37.30)
19 to 44	16,001	(35.24)	7,827	(30.23)
45 to 74	6,697	(14.75)	4,039	(15.60)
75 and older	806	(1.78)	785	(3.03)
Female	22,720	(50.04)	13,998	(54.06)
Education of household head				
No schooling	15,081	(33.24)	8,537	(32.99)
Up to primary	11,551	(25.46)	6,157	(23.79)
More than primary	18,733	(41.29)	11,187	(43.22)
Household head is self-employed	34,562	(80.28)	19,473	(78.97)
Expenditure quintiles				
Poorest	14,001	(30.84)	7,347	(28.37)
Poorer	9,305	(20.40)	5,626	(21.73)
Middle	8,070	(17.77)	4,835	(18.67)
Richer	7,323	(16.13)	4,246	(16.40)
Richest	6,706	(14.77)	3,840	(14.83)
Health need and medical care utilization (2 weeks)				
Illness or injury	6,149	(13.56)	4,162	(16.10)
Stopped activities due to severity	3,692	(59.99)	2,697	(64.61)
Sought care due to illness or injury	3,699	(60.16)	3,131	(75.23)
OOP health expenditure by quintile				
All households	6,391	(56.60)	2,993	(54.90)
Poor	1,234	(19.31)	484	(16.17)
Poorer	1,197	(18.73)	554	(18.51)
Middle	1,224	(19.15)	604	(20.18)
Richer	1,256	(19.65)	615	(20.55)
Richest	1,480	(23.16)	736	(24.59)
Catastrophic OOP payments absorb >10% of non-food household consumption				
All households	552	(4.62)	232	(4.26)
Poorest	145	(1.28)	43	(0.79)
Poorer	132	(1.17)	43	(0.79)
Middle	108	(0.96)	51	(0.94)
Richer	91	(0.81)	50	(0.92)
Richest	76	(1.19)	45	(0.83)
Hospital > 1hr*	12,545	(46.64)	5,503	(33.50)
Rural residence	27,919	(61.49)	16,239	(62.71)

*Merged from Section 42 of the GLSS 6 Community questionnaire, which collected information on distance to health facilities using a reduced sample of 44,056 individuals within 643 clusters.

Table 2. Utilization results using probit models with unmatched data, propensity score matched data (PSM) and matched data with instrumental variable (PSM-IV), Ghana 2012-2013

	Medical care when ill or injured			
	(1) Unmatched	(2) PSM	(3) First-stage PSM-IV	(4) PSM-IV
NHIS	0.43***	0.43***	.	0.22***
	(0.36 - 0.50)	(0.35 - 0.51)		(0.05 - 0.39)
Cluster insurance rate			0.98***	
			(0.93 - 1.02)	
Age categories				
Under 5			(Reference)	
5 to 18	-0.30***	-0.30***	-0.03	-0.30***
	(-0.40 - -0.20)	(-0.41 - -0.18)	(-0.06 - 0.01)	(-0.41 - -0.19)
19 to 44	-0.30***	-0.28***	-0.10***	-0.30***
	(-0.40 - -0.19)	(-0.39 - -0.16)	(-0.13 - -0.06)	(-0.41 - -0.18)
45 to 74	-0.34***	-0.34***	-0.03	-0.34***
	(-0.45 - -0.23)	(-0.46 - -0.21)	(-0.06 - 0.01)	(-0.46 - -0.21)
75 and older	-0.35***	-0.28***	0.06*	-0.27**
	(-0.54 - -0.16)	(-0.49 - -0.07)	(-0.00 - 0.13)	(-0.48 - -0.05)
Female	0.06*	0.05	0.02	0.04
	(-0.00 - 0.13)	(-0.10 - 0.19)	(-0.02 - 0.07)	(-0.10 - 0.19)
Female household head	-0.05	-0.08	0.00	-0.08
	(-0.14 - 0.03)	(-0.19 - 0.03)	(-0.03 - 0.04)	(-0.18 - 0.03)
Education of household head				
No schooling			(Reference)	
Up to primary	0.07	0.08*	0.02	0.09*
	(-0.02 - 0.15)	(-0.01 - 0.18)	(-0.02 - 0.05)	(-0.01 - 0.18)
More than primary	0.08	0.04	0.05***	0.05
	(-0.02 - 0.17)	(-0.08 - 0.15)	(0.02 - 0.09)	(-0.06 - 0.16)
Household head is self-employed	0.07	-0.02	0.01	-0.01
	(-0.04 - 0.19)	(-0.15 - 0.11)	(-0.04 - 0.05)	(-0.15 - 0.12)
Expenditure quintiles				
Poorest			(Reference)	
Poorer	0.16***	0.15***	0.03	0.16***
	(0.07 - 0.25)	(0.04 - 0.26)	(-0.01 - 0.06)	(0.05 - 0.27)
Middle	0.21***	0.22***	0.03	0.22***
	(0.10 - 0.31)	(0.08 - 0.36)	(-0.01 - 0.07)	(0.08 - 0.36)
Richer	0.27***	0.26***	0.03	0.26***
	(0.15 - 0.40)	(0.08 - 0.44)	(-0.03 - 0.09)	(0.08 - 0.44)
Richest	0.29***	0.25**	0.05	0.26**
	(0.14 - 0.44)	(0.02 - 0.48)	(-0.01 - 0.12)	(0.03 - 0.49)

Table 2. (continued)

	Medical care when ill or injured			
	(1) Unmatched	(2) PSM	(3) First-stage PSM-IV	(4) PSM-IV
Household size	0.01	0.01	0.00	0.00
	(-0.00 - 0.02)	(-0.01 - 0.03)	(-0.01 - 0.01)	(-0.02 - 0.02)
Severity of illness or injury	0.45***	0.45***	0.01	0.45***
	(0.38 - 0.52)	(0.31 - 0.59)	(-0.03 - 0.05)	(0.30 - 0.59)
Hospital > 1hr	-0.08**	-0.08	0.07*	-0.07
	(-0.15 - -0.01)	(-0.36 - 0.19)	(-0.01 - 0.16)	(-0.34 - 0.20)
Rural residence	-0.20**	-0.27	0.13***	-0.23
	(-0.36 - -0.04)	(-0.62 - 0.09)	(0.03 - 0.23)	(-0.58 - 0.12)
Observations	6,307	4,920	4,920	4,920
Controls and Region FE included	YES	YES	YES	YES
Wald test p-value			<0.001	

*** p<0.01, ** p<0.05, * p<0.1. Robust 95% Confidence Intervals in parentheses. Controls include ten region dummies, disability, cohabitation with elderly members and radio ownership.

Table 3. Financial risk protection results using probit models with unmatched data, propensity score matched data (PSM) and matched data with instrumental variable (PSM-IV), Ghana 2012-2013

	OOP payment exceeds 10% of non-food consumption			
	(1) Unmatched	(2) PSM	(3) First-stage PSM-IV	(4) PSM-IV
NHIS	-0.14***	-0.12***		-0.47***
	(-0.19 - -0.09)	(-0.19 - -0.05)		(-0.66 - -0.29)
Cluster insurance rate			0.79***	
			(0.76 - 0.82)	
Age of household head	0.00*	0.00	-0.00***	0.00
	(-0.00 - 0.00)	(-0.00 - 0.01)	(-0.00 - -0.00)	(-0.00 - 0.01)
Female household head	0.16***	0.30***	0.00	0.29***
	(0.10 - 0.23)	(0.19 - 0.40)	(-0.03 - 0.03)	(0.19 - 0.40)
Education of household head				
No schooling			(Reference)	
Up to primary	-0.05	0.04	0.00	0.04
	(-0.10 - 0.01)	(-0.06 - 0.14)	(-0.02 - 0.03)	(-0.06 - 0.14)
More than primary	-0.06*	0.09	0.04**	0.10
	(-0.13 - 0.00)	(-0.07 - 0.24)	(0.00 - 0.08)	(-0.06 - 0.26)
Household head is self-employed	0.01	0.08	0.07***	0.10
	(-0.08 - 0.10)	(-0.09 - 0.25)	(0.03 - 0.10)	(-0.06 - 0.27)
Expenditure quintiles				
Poorest			(Reference)	
Poorer	-0.07**	-0.03	0.02*	-0.02
	(-0.13 - -0.01)	(-0.12 - 0.07)	(-0.00 - 0.04)	(-0.12 - 0.07)
Middle	-0.28***	-0.25***	0.03*	-0.25***
	(-0.36 - -0.21)	(-0.38 - -0.12)	(-0.00 - 0.06)	(-0.38 - -0.11)
Richer	-0.33***	-0.34***	0.01	-0.34***
	(-0.42 - -0.24)	(-0.52 - -0.16)	(-0.03 - 0.05)	(-0.52 - -0.16)
Richest	-0.63***	-0.48***	-0.04	-0.49***
	(-0.75 - -0.50)	(-0.71 - -0.26)	(-0.09 - 0.01)	(-0.72 - -0.27)
Household size	-0.07***	-0.05***	-0.00	-0.05***
	(-0.08 - -0.06)	(-0.07 - -0.04)	(-0.01 - 0.00)	(-0.07 - -0.04)
Hospital > 1hr	0.03	0.04	0.15***	0.09
	(-0.02 - 0.08)	(-0.35 - 0.43)	(0.06 - 0.24)	(-0.30 - 0.48)
Rural residence	0.20***	-0.03	0.18***	0.02
	(0.07 - 0.33)	(-0.35 - 0.29)	(0.10 - 0.26)	(-0.31 - 0.34)
Observations	25,971	12,684	12,684	12,684
Catastrophic OOP observations	2,089	936	936	936
Non-Catastrophic OOP observations	23,882	11,748	11,748	11,748
Controls and region FE included	YES	YES	YES	YES
Wald test p-value			<0.001	

*** p<0.01, ** p<0.05, * p<0.1. Robust 95% Confidence Intervals in parentheses. Controls include ten region dummies, disability, disease severity, cohabitation with elderly members and radio ownership.

Table 4. Financial risk protection results using outcome variables derived from the unified financial risk protection methodology, Ghana 2012-2013

	Poor households♀			Non-poor households✧					
	Log OOP immiseration burden on household discretionary consumption			OOP payments absorb >25% of household discretionary consumption			OOP payments leave household consumption below 110% of the poverty line		
	(1) Unmatched	(2) PSM	(3) PSM-IV	(4) Unmatched	(5) PSM	(6) PSM-IV	(7) Unmatched	(8) PSM	(9) PSM-IV
NHIS	-0.14***	-0.06	-0.31**	-0.14***	-0.13**	-0.57***	0.07**	-0.17***	-0.33**
	(-0.19 - -0.08)	(-0.13 - 0.02)	(-0.56 - -0.07)	(-0.23 - -0.06)	(-0.26 - -0.01)	(-0.91 - -0.23)	(0.00 - 0.13)	(-0.27 - -0.07)	(-0.64 - -0.02)
Cluster insurance (First-stage)			0.68***			0.74***			0.72***
			(0.63 - 0.73)			(0.68 - 0.79)			(0.66 - 0.78)
Observations	13,645	5,780	5,780	12,080	5,038	5,038	10,542	4,161	4,161
R-squared	0.30	0.29	0.29						
F-statistic p-value			<0.001						
Wald test p-value						0.01			0.30

*** p<0.01, ** p<0.05, * p<0.1. Robust 95% Confidence Intervals in parentheses. ♀ Households that were below the poverty line prior to incurring OOP health spending. ✧Households that were above the poverty line prior to incurring OOP health spending. Columns (1) through (3) show linear regression models. Columns (4) through (9) show probit models. All specifications include controls and region fixed effects. Controls include ten region dummies, age, gender, education and employment status of household head, household consumption expenditure quintiles, household size, distance to nearest hospital, rural residence, disability, disease severity, cohabitation with elderly members and radio ownership.

Table 5. Effect estimates of health insurance on medical utilization and financial risk protection by distance to nearest hospital using IV-probit models and propensity score matched datasets, Ghana 2012-2013

	Local Average Treatment Effect	
	Medical care utilization when ill or injured	OOP payment exceeds 10% of non-food consumption
	(1) PSM-IV Probit	(2) PSM-IV Probit
All individuals	**0.15***** (0.13–0.18) 4,920	**-0.07***** (-0.10 – -0.03) 12,684
Individuals living *within* 1 hour-radius to nearest hospital	**0.17***** (0.13–0.20) 3,003	**-0.09***** (-0.13 – -0.05) 7,803
Individuals living *outside* 1 hour-radius to nearest hospital	**0.14***** (0.09–0.18) 1,917	**-0.05**** (-0.09 – -0.004) 4,881
(T-statistic p-value)	(0.15)	(0.07)

*** p<0.01, ** p<0.05, * p<0.1. Numbers in bold are estimated effects. 95% Confidence Intervals in parentheses. Last number in each cell is the sample size.

Table 6. Bootstrapped local average treatment effect (LATE) estimates of health insurance on medical care utilization using IV-probit models and propensity score matched datasets, Ghana 2012-2013

	Household consumption expenditure		Education of household head		Employment of household head	
	(1)	(2)	(3)	(4)	(5)	(6)
	Poorest 40%	Richest 40%	Up to primary	> Primary	Self-employed	Employed
All individuals	**0.18***** (0.14–0.21) 2,921	**0.08**** (0.02–0.14) 1,054	**0.17***** (0.14–0.19) 3,309	**0.13***** (0.07–0.19) 1,627	**0.15***** (0.12–0.18) 4,381	**0.16***** (0.07–0.25) 555
(T-statistic p-value)	(0.003)		(0.11)		(0.41)	
	Distance and Poverty		*Distance and Education*		*Distance and Employment*	
Individuals living *within* 1 hour-radius to nearest hospital	**0.20***** (0.16–0.25) 1,589	**0.09**** (0.02–0.15) 761	**0.18***** (0.13–0.22) 1,863	**0.15***** (0.10–0.21) 1,132	**0.17***** (0.13–0.21) 2,573	**0.14***** (0.04–0.25) 422
Individuals living *outside* 1 hour-radius to nearest hospital	**0.15***** (0.09–0.21) 1,332	**0.10** (-0.04–0.23) 293	**0.16***** (0.11–0.20) 1,446	**0.08*** (-0.01–0.17) 495	**0.13***** (0.08–0.17) 1,808	**0.42** (-0.08–0.92) 119
(T-statistic p-value)♀	(0.07)	(0.44)	(0.25)	(0.09)	(0.08)	(0.053)

*** p<0.01, ** p<0.05, * p<0.1. Numbers in bold are estimated effects. 95% Confidence Intervals in parentheses. Last number in each cell is the sample size. ♀ P-values from T-statistics correspond to effect differences between rows 2 and 3.

Table 7. Bootstrapped local average treatment effect (LATE) estimates of health insurance on catastrophic out-of-pocket health expenditure using IV-probit models and propensity score matched datasets, Ghana 2012-2013

	Household consumption expenditure		Education of household head		Employment of household head	
	(1)	(2)	(3)	(4)	(5)	(6)
	Poorest 40%	Richest 40%	Up to primary	> Primary	Self-employed	Employed
All individuals	**-0.10***** (-0.14 – -0.07) 7,624	**-0.06**** (-0.10 – -0.01) 2,336	**-0.03*** (-0.07 – 0.003) 8,603	**-0.14***** (-0.18 – -0.09) 4,081	**-0.06***** (-0.09 – -0.03) 11,471	**-0.16**** (-0.32 – -0.01) 927
(T-statistic p-value)	(0.10)		(<0.001)		(0.04)	
	Distance and Poverty		*Distance and Education*		*Distance and Employment*	
Individuals living *within* 1 hour-radius to nearest hospital	**-0.13***** (-0.18 – -0.07) 4,465	**-0.04** (-0.08 – 0.01) 1,603	**-0.07***** (-0.11 – -0.02) 5,145	**-0.16***** (-0.22 – -0.10) 2,630	**-0.09***** (-0.13 – -0.04) 6,881	**-0.13** (-0.35 – 0.10) 851
Individuals living *outside* 1 hour-radius to nearest hospital	**-0.07**** (-0.12 – -0.01) 3,128	**-0.24**** (-0.44 – -0.04) 474	**-0.02** (-0.07 – 0.04) 3,407	**-0.19***** (-0.31 – -0.08) 1,182	**-0.04** (-0.09 – 0.02) 4,519	**-0.26***** (-0.39 – -0.13) 362
(T-statistic p-value)ᵠ	(0.06)	(0.002)	(0.07)	(0.29)	(0.08)	(0.24)

*** p<0.01, ** p<0.05, * p<0.1. Numbers in bold are estimated effects. 95% Confidence Intervals in parentheses. Last number in each cell is the sample size. ᵠP-values from T-statistics correspond to effect differences between rows 2 and 3.

Table 8. Average treatment effects on the treated (ATT) across matching methods, Ghana 2012-2013

	Medical utilization				Catastrophic health expenditure			
	N treated	N control	ATT	95% CI	N treated	N control	ATT	95% CI
Nearest-neighbour	2,468	2,476	0.155***	(0.131 – 0.180)	6,342	6,532	-0.022***	(-0.026 – -0.018)
Radius	2,617	3,605	0.155***	(0.130 – 0.179)	9,024	13,881	-0.023***	(-0.033 – -0.014)
Kernel	2,666	3,641	0.157***	(0.134 – 0.181)	9,615	16,356	-0.026***	(-0.033 – -0.019)
Mahalanobis	2,666	3,641	0.145***	(0.114 – 0.175)	9,615	16,356	-0.006	(-0.013 – 0.002)

*** p<0.01, ** p<0.05, * p<0.1. CI: Confidence intervals

Figure 1. Distribution of propensity scores using nearest neighbour matching for medical utilization across treatment and comparison groups and representation of standardized bias between matched and unmatched samples, Ghana 2012-2013

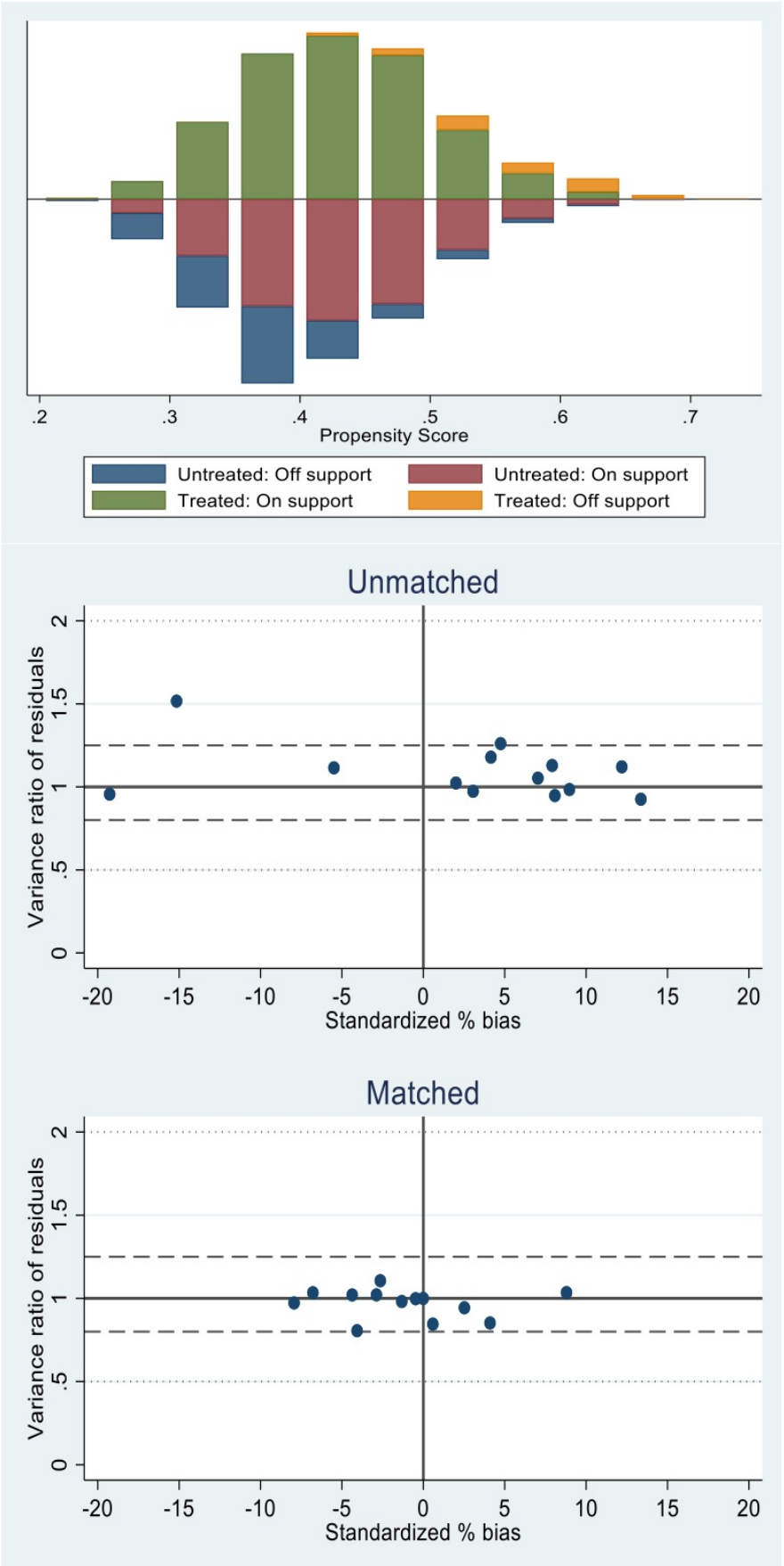
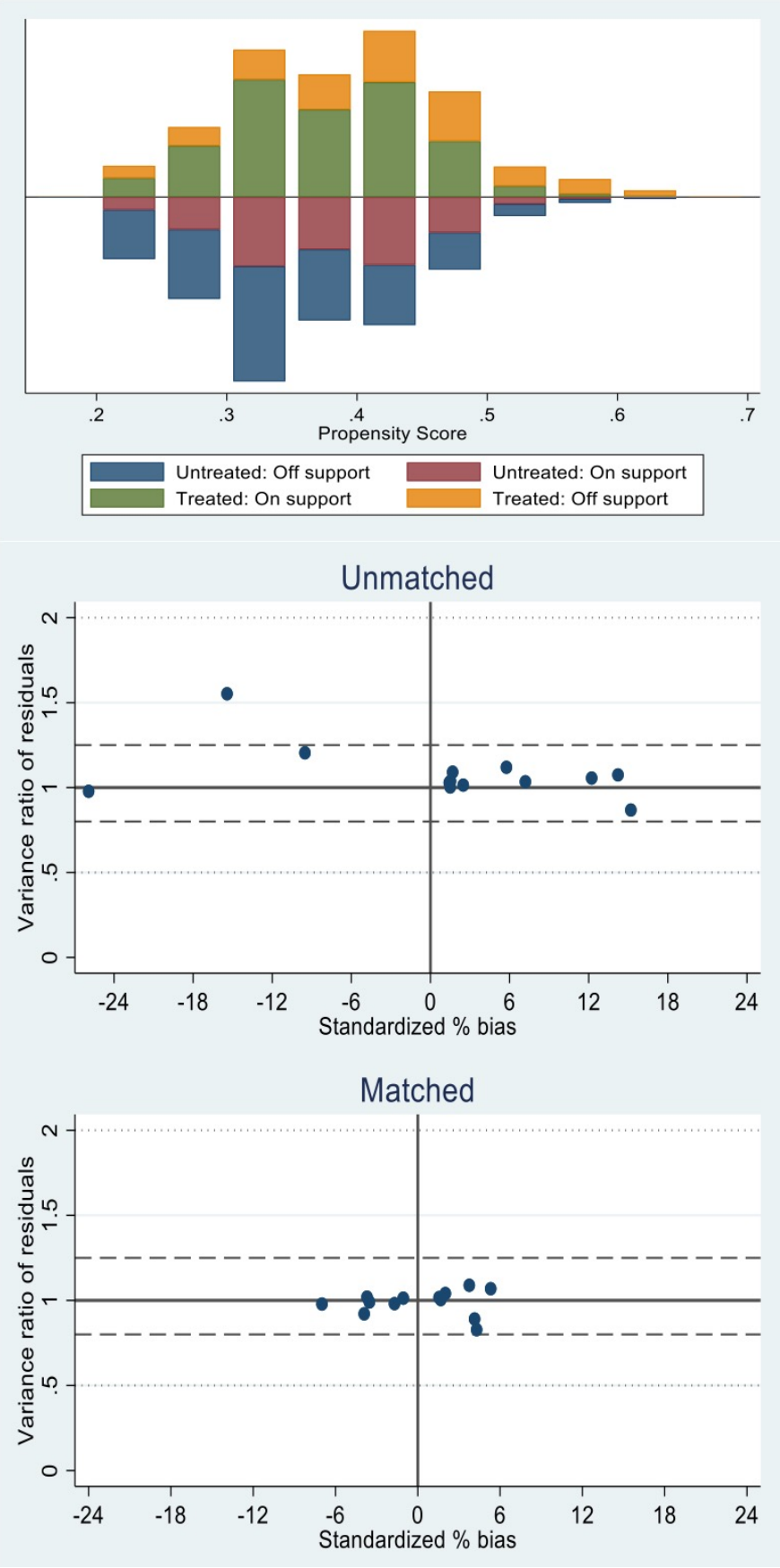


Figure 2. Distribution of propensity scores using nearest neighbour matching for financial risk protection across treatment and comparison groups and representation of standardized bias between matched and unmatched samples, Ghana 2012-2013



Appendix A: Balancing properties test for propensity score matching

Table A1. Test of the balancing property of the propensity score for medical care utilization, Ghana 2012-2013

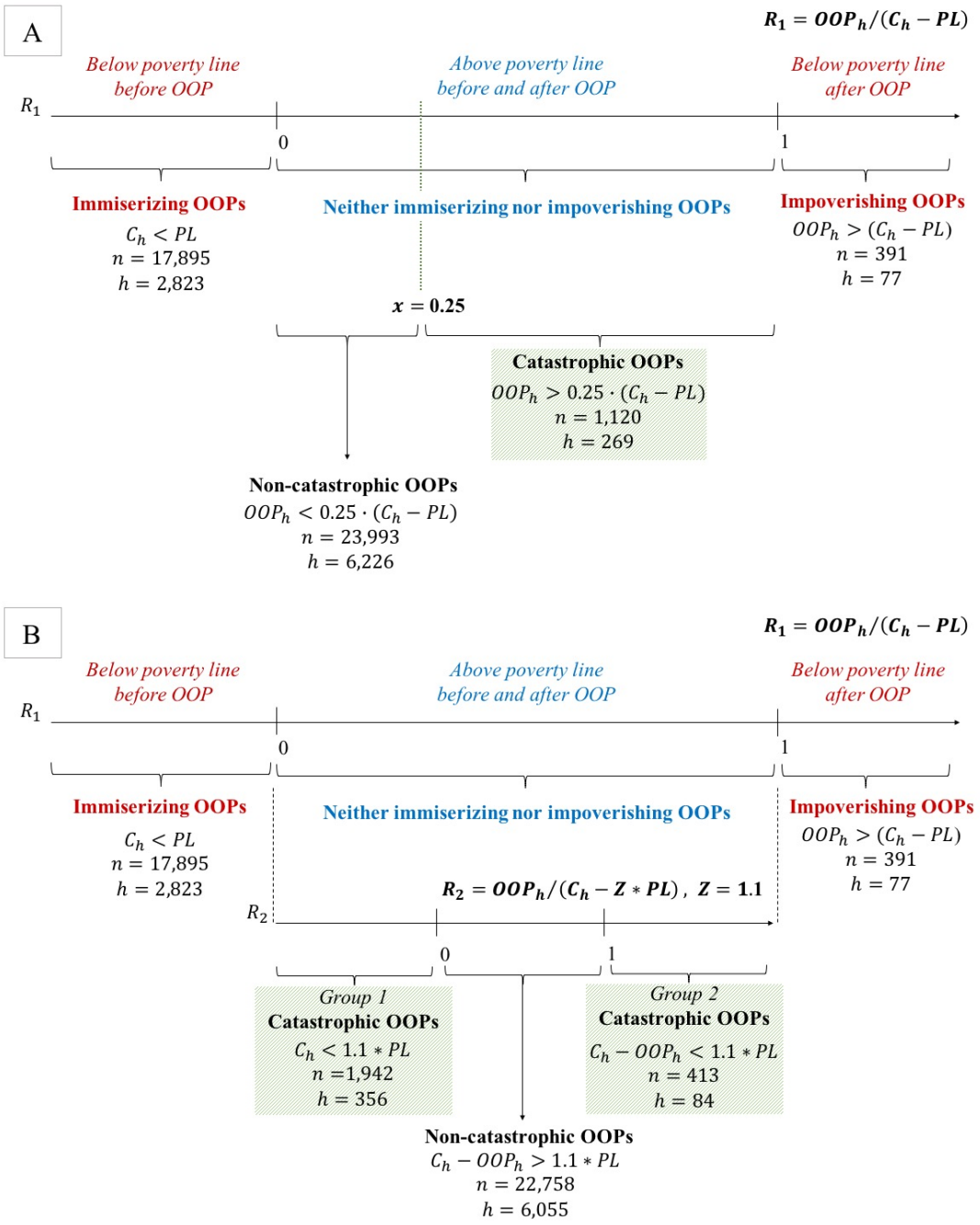
	Mean		% reduction		
	Insured	Uninsured	% bias	bias	p>|t|
Age (years)					
Unmatched	28.32	27.32	4.2		0.10
Matched	27.90	28.53	-2.6	36.4	0.39
Gender					
Unmatched	0.57	0.52	9		<0.001
Matched	0.55	0.56	-0.5	94.7	0.88
Gender of head					
Unmatched	0.22	0.21	2		0.43
Matched	0.22	0.22	-1.3	33.9	0.66
Education of head					
Unmatched	1.00	0.94	7		0.01
Matched	0.98	1.00	-2.9	59.1	0.34
Head self-employed					
Unmatched	0.88	0.89	-5.5		0.03
Matched	0.89	0.88	2.5	54.1	0.40
Rural					
Unmatched	1.92	1.95	-15.2		<0.001
Matched	1.95	1.94	4.1	73	0.16
Household size					
Unmatched	5.96	5.85	3.1		0.23
Matched	5.97	5.95	0.6	80.9	0.85
Elderly household member					
Unmatched	0.22	0.19	7.9		<0.001
Matched	0.21	0.21	0	99.9	1.00
Expenditure (quintiles)					
Unmatched	2.41	2.25	12.2		<0.001
Matched	2.35	2.44	-6.8	44.4	0.03
Hospital > 1hr					
Unmatched	0.37	0.46	-19.3		<0.001
Matched	0.39	0.35	8.8	54.4	<0.001
Radio ownership					
Unmatched	0.70	0.64	13.4		<0.001
Matched	0.69	0.72	-7.9	40.6	0.01
Severity of illness or injury					
Unmatched	0.67	0.63	8.1		<0.001
Matched	0.66	0.68	-4.4	45.9	0.15
Disability					
Unmatched	0.04	0.03	4.7		0.06
Matched	0.03	0.04	-4.1	14.3	0.17

Table A2. Test of the balancing property of the propensity score for catastrophic out-of-pocket health expenditure, Ghana 2012-2013

	Mean		% reduction		
	Insured	Uninsured	% bias	bias	p>|t|
Age of head (years)					
Unmatched	48.93	47.86	7.2		<0.001
Matched	48.10	48.67	-3.9	45.7	0.05
Gender of head					
Unmatched	0.17	0.16	1.4		0.27
Matched	0.17	0.18	-1.7	-19.3	0.40
Education of head					
Unmatched	0.99	0.89	12.2		<0.001
Matched	0.97	0.95	2	83.5	0.31
Head self-employed					
Unmatched	0.88	0.91	-9.5		<0.001
Matched	0.91	0.89	4.1	56.5	0.03
Rural					
Unmatched	1.92	1.96	-15.4		<0.001
Matched	1.96	1.95	4.3	72.2	0.01
Household size					
Unmatched	6.85	6.79	1.7		0.19
Matched	6.62	6.57	1.6	7.7	0.42
Elderly household member					
Unmatched	0.19	0.17	5.8		<0.001
Matched	0.19	0.18	1.7	70.9	0.40
Expenditure (quintiles)					
Unmatched	2.41	2.23	14.2		<0.001
Matched	2.31	2.40	-7	50.9	<0.001
Hospital > 1hr					
Unmatched	0.34	0.47	-25.9		<0.001
Matched	0.39	0.36	5.3	79.5	0.01
Radio ownership					
Unmatched	0.74	0.67	15.2		<0.001
Matched	0.73	0.73	-1.1	93	0.59
Household member sick or injured					
Unmatched	0.57	0.56	1.5		0.24
Matched	0.57	0.59	-3.7	-146.9	0.06
Household member severely sick or injured					
Unmatched	0.43	0.42	2.5		0.05
Matched	0.44	0.45	-3.5	-41.9	0.08
Household member with disability					
Unmatched	0.10	0.09	1.5		0.24
Matched	0.10	0.09	3.8	-147.2	0.06

Appendix B: Unified financial risk protection classification

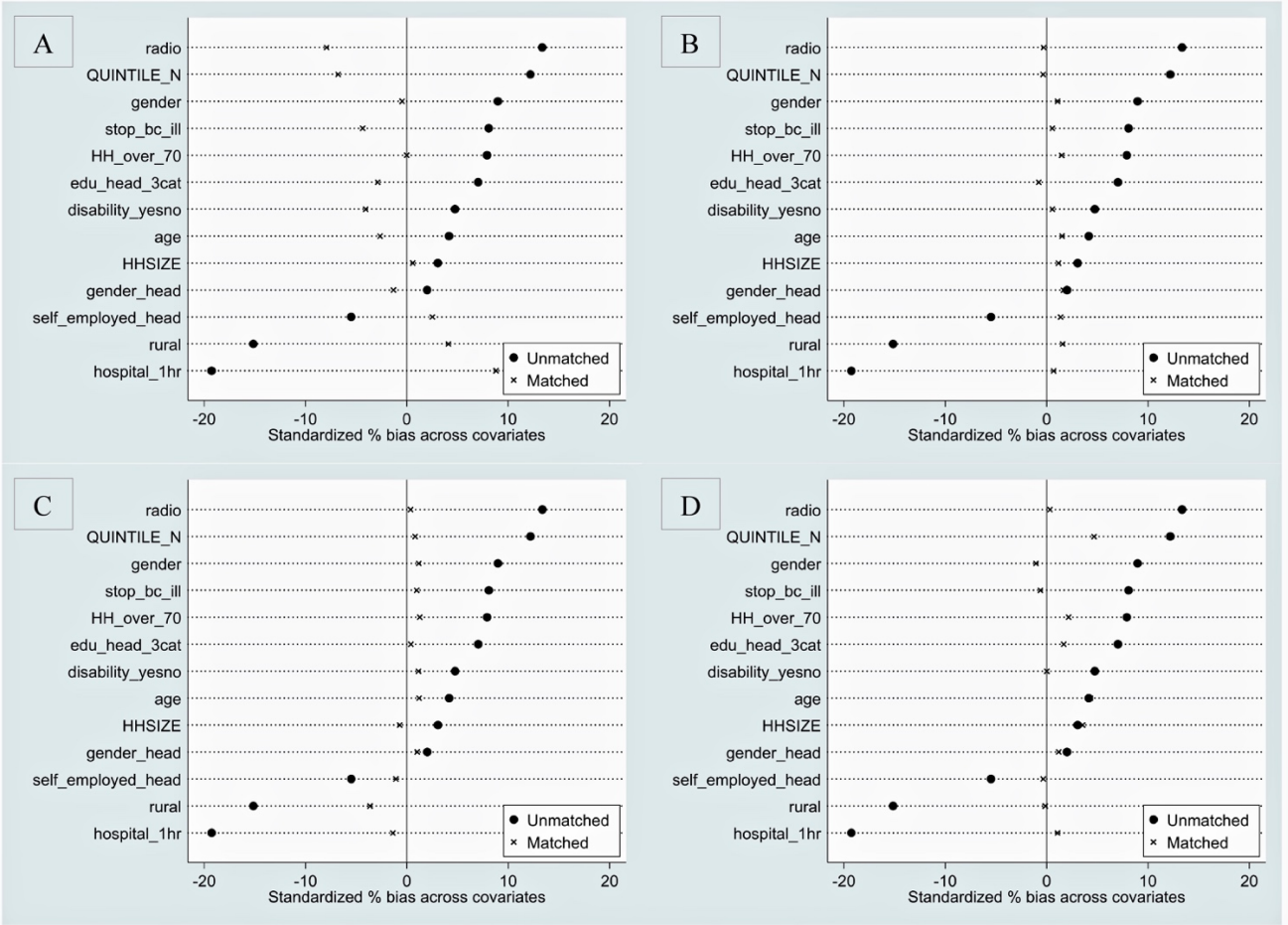
Figure B1. Classification of out-of-pocket expenditure categories for robustness checks



The figure shows the classification of out-of-pocket (OOP) health payments derived from Wagstaff and Eozenou's unified financial risk protection methodology (2014) with the number of individuals (n) and households (h) identified in each category. OOP health payments are expressed as a ratio R_1 of discretionary consumption, obtained by deducting the poverty line (PL) from each household's total annual real consumption expenditure (C_h): $R_1 = OOP_h/(C_h - PL)$. We used the absolute poverty line in Ghana, which equals 1,314 Ghana Cedis (US$ 270) per adult annually. Households impoverished by OOP payments are those for whom $R_1 > 1$, and households who are immiserized by OOP payments are those for whom $R_1 < 0$. The remaining category of households who are neither impoverished nor immiserized by OOP expenditure are above the poverty line prior to incurring OOP payments ($C_h - PL > 0$) and remain above it even after incurring them ($C_h - OOP > PL$). These families are classified into those who experience catastrophic payments, and those who do not, based on the values of two ratios: R_1, and $R_2 = OOP_h/(C_h - Z \cdot PL)$. We used a threshold ($x = 0.25$) of what can be considered an 'excessive size' of the ratio R_1 (Panel A) and set a pre-specified multiple of the poverty line ($Z = 1.1$) denoting 'excessive closeness' to impoverishment based on the ratio R_2 (Panel B).

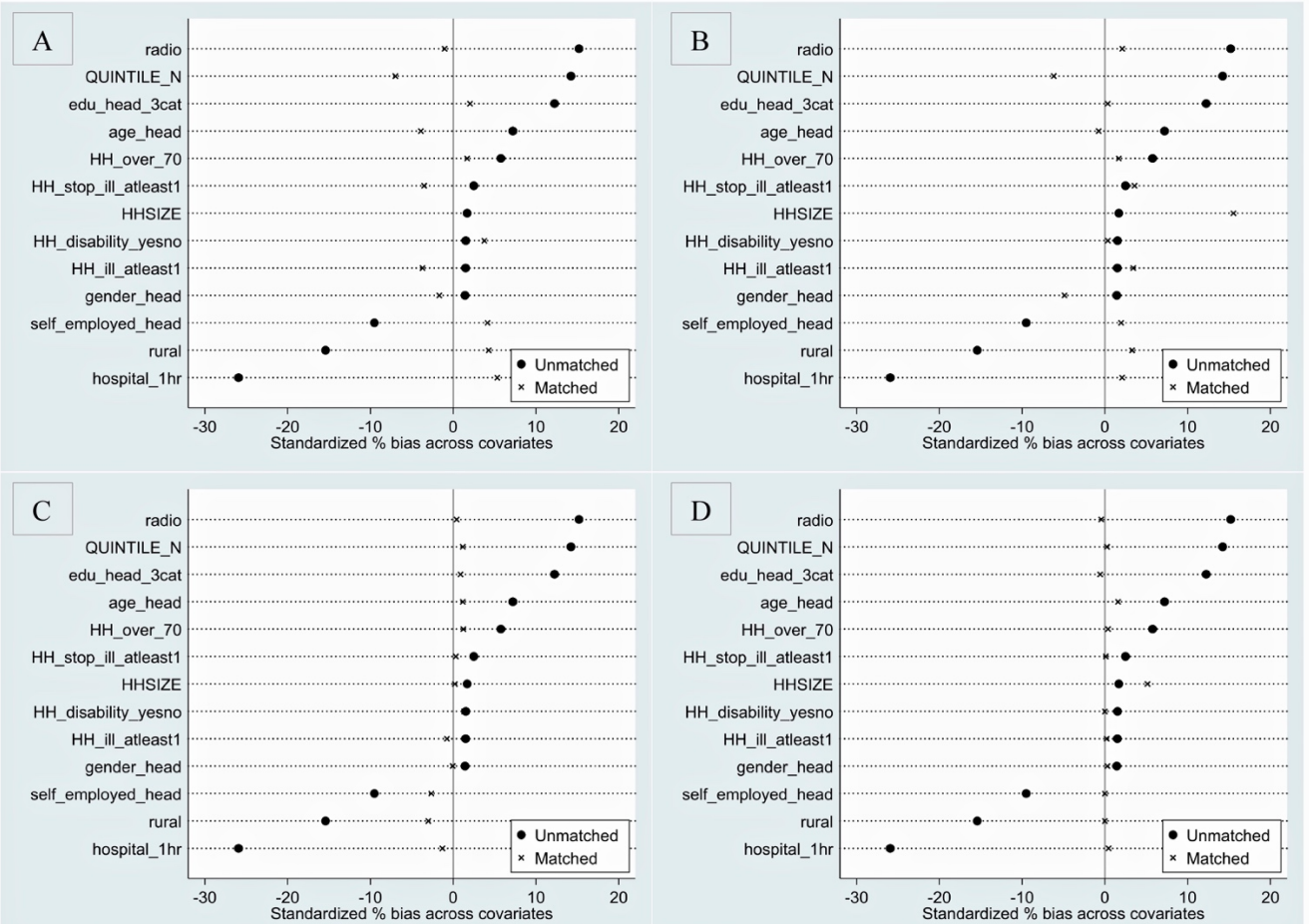
Appendix C: Standardized bias tests for propensity score matching

Figure C1. Standardized bias across covariates between matched and unmatched samples for the medical utilization outcome variable using different matching methods, Ghana 2012-2013



Panel A: Nearest neighbor matching without replacement, Panel B: Radius matching, Panel C: Kernel matching, Panel D: Mahalanobis matching. *Variable labels:* 'radio'= radio ownership, 'QUINTILE_N'= household consumption expenditure quintiles, 'gender'= gender of respondent, 'stop_bc_ill' = severity of illness or injury, 'HH_over_70' = cohabitation with elderly household member, 'edu_head_3cat' = highest level of education attained by the household head, 'disability_yesno' = disability status of respondent, 'age' = age of respondent, 'HHSIZE' = household size, 'gender_head' = gender of household head, 'self_employed_head' = head of household is self-employed, 'rural' = rural residence, 'hospital_1hr' = respondent lives outside one-hour travel distance to the nearest hospital.

Figure C2. Standardized bias across covariates between matched and unmatched samples for the financial risk protection outcome variable using different matching methods, Ghana 2012-2013



Panel A: Nearest neighbor matching without replacement, Panel B: Radius matching, Panel C: Kernel matching, Panel D: Mahalanobis matching. *Variable labels:* 'radio'= radio ownership, 'QUINTILE_N'= household consumption expenditure quintiles, 'edu_head_3cat' = highest level of education attained by the household head, 'age_head' = age of household head, 'HH_over_70' = cohabitation with elderly household member, 'HH_stop_ill_atleast1' = At least one household member has suffered a severe illness of injury, 'HHSIZE' = household size, 'HH_disability_yesno' = At least one member of the household lives with a disability, 'HH_ill_atleast1' = At least one member of the household has been ill or injured, 'gender_head' = gender of the household head, 'self_employed_head' = head of household is self-employed, 'rural' = rural residence, 'hospital_1hr' = respondent lives outside one-hour travel distance to the nearest hospital.

Appendix D: Simulation-based sensitivity analysis for propensity scores

Table D1. Sensitivity analysis of the propensity score for medical care utilization: effect of 'calibrated' confounders, Ghana 2012-2013

	Fraction $U = 1$ by treatment / outcome				Outcome effect Γ	Selection effect Λ	ATT	95% CI
	p11	*p10*	*p01*	*p00*				
No confounder	0.00	0.00	0.00	0.00	-	-	0.15	(0.12–0.18)
Neutral confounder	0.50	0.50	0.50	0.50	1.00	1.00	0.16	(0.12–0.19)
Confounder-like								
Female	0.58	0.58	0.55	0.52	1.13	1.16	0.15	(0.11–0.19)
Female household head	0.26	0.28	0.27	0.25	1.09	1.02	0.15	(0.11–0.19)
Self-employed household head	0.80	0.85	0.80	0.83	0.79	0.99	0.15	(0.12–0.19)
Rural residence	0.65	0.68	0.61	0.67	0.75	1.12	0.15	(0.12–0.19)
Elderly household member	0.20	0.22	0.14	0.17	0.85	1.44	0.16	(0.12–0.20)
Hospital > 1hr	0.33	0.42	0.42	0.49	0.79	0.67	0.15	(0.11–0.19)
Radio ownership	0.70	0.66	0.65	0.62	1.11	1.26	0.16	(0.12–0.19)
Severity of illness or injury	0.69	0.50	0.65	0.52	1.75	1.22	0.15	(0.11–0.19)
Disability	0.04	0.04	0.03	0.03	0.83	1.34	0.16	(0.12–0.19)

Note: Let U be a binary confounding factor whose distribution is fully characterized by the choice of four parameters, $p_{ij} = \Pr(U = 1 | T = i, Y = j$ with $i, j \in \{0,1\}$. This gives the probability that $U=1$ in each of the four groups defined by treatment and outcome. Given these parameters, we predict a value of U for each treated and control subject and re-estimate the ATT by nearest neighbour propensity score matching including the simulated U in the set of matching variables W. The process is repeated 100 times. Γ denotes the average estimated odds ratio of U in the logit model of $\Pr(Y = 1 | T = 0, U, W)$. Λ is the average estimated odds ratio of U in the logit model of $\Pr(T = 1, U, W)$. ATT is the average of the simulated ATTs. CI is the confidence interval. The first row shows the ATT estimate with no confounding factor U. The second row shows the ATT estimate with a confounding factor U whose outcome and selection effect are insignificant. In each confounder-like row, U has been calibrated to match the distribution of the corresponding variable.

Table D2. Sensitivity analysis of the propensity score for catastrophic health expenditure: effect of 'calibrated' confounders, Ghana 2012-2013

	Fraction $U = 1$ by treatment / outcome				Outcome effect Γ	Selection effect Λ	ATT	95% CI
	p11	*p10*	*p01*	*p00*				
No confounder	0.00	0.00	0.00	0.00	-	-	-0.02	(-0.03 – -0.01)
Neutral confounder	0.50	0.50	0.50	0.50	1.00	1.00	-0.03	(-0.04 – -0.01)
Confounder-like								
Female household head	0.35	0.20	0.27	0.21	1.37	0.99	-0.02	(-0.04 – -0.01)
Self-employed household head	0.90	0.81	0.88	0.82	1.57	0.92	-0.02	(-0.04 – -0.01)
Rural residence	0.73	0.64	0.74	0.63	1.67	1.04	-0.02	(-0.04 – -0.01)
Elderly household member	0.26	0.18	0.18	0.15	1.31	1.24	-0.03	(-0.04 – -0.01)
Hospital > 1hr	0.36	0.33	0.48	0.46	1.08	0.59	-0.03	(-0.04 – -0.01)
Radio ownership	0.63	0.73	0.62	0.68	0.75	1.25	-0.02	(-0.04 – -0.01)
Household member sick/injured	0.64	0.52	0.57	0.52	1.23	1.04	-0.03	(-0.04 – -0.01)
Household member severely sick/injured	0.48	0.39	0.42	0.37	1.27	1.09	-0.03	(-0.04 – -0.01)
Household member with disability	0.17	0.09	0.15	0.08	1.95	1.04	-0.03	(-0.04 – -0.01)

Note: Let U be a binary confounding factor whose distribution is fully characterized by the choice of four parameters, $p_{ij} = \Pr(U = 1 | T = i, Y = j$ with $i, j \in \{0,1\}$. This gives the probability that $U=1$ in each of the four groups defined by treatment and outcome. Given these parameters, we predict a value of U for each treated and control subject and re-estimate the ATT by nearest neighbour propensity score matching including the simulated U in the set of matching variables W. The process is repeated 100 times. Γ denotes the average estimated odds ratio of U in the logit model of $\Pr(Y = 1 | T = 0, U, W)$. Λ is the average estimated odds ratio of U in the logit model of $\Pr(T = 1, U, W)$. ATT is the average of the simulated ATTs. CI is the confidence interval. The first row shows the ATT estimate with no confounding factor U. The second row shows the ATT estimate with a confounding factor U whose outcome and selection effect are insignificant. In each confounder-like row, U has been calibrated to match the distribution of the corresponding variable.

Table D3. Sensitivity analysis of the propensity score for medical care utilization: characterizing 'killer' confounders, Ghana 2012-2013

	$s = 0.1$ $\Lambda \in [1.3, 1.4]$	$s = 0.2$ $\Lambda \in [1.9, 2.2]$	$s = 0.3$ $\Lambda \in [2.8, 3.6]$	$s = 0.4$ $\Lambda \in [4.4, 6.7]$	$s = 0.5$ $\Lambda \in [7.4, 12.3]$	$s = 0.6$ $\Lambda \in [17.4, 31.0]$
$d = 0.1$ $\Gamma \in [1.5]$	0.15 (0.11–0.18)	0.14 (0.10–0.18)	0.13 (0.09–0.17)	0.12 (0.07–0.16)	0.11 (0.06–0.16)	0.11 (0.05–0.16)
$d = 0.2$ $\Gamma \in [2.3]$	0.14 (0.10–0.18)	0.12 (0.08–0.16)	0.10 (0.06–0.14)	0.08 (0.04–0.13)	0.06 (0.02–0.11)	0.06 (0.01–0.10)
$d = 0.3$ $\Gamma \in [3.6, 3.8]$	0.14 (0.10–0.18)	0.11 (0.07–0.14)	0.08 (0.04–0.12)	0.05 (0.004–0.09)	0.02 (-0.03–0.06)	-0.01 (-0.05–0.04)
$d = 0.4$ $\Gamma \in [7.0, 7.1]$	0.13 (0.09–0.17)	0.09 (0.05–0.13)	0.05 (0.01–0.09)	0.01 (-0.03–0.05)	-0.03 (-0.07–0.02)	-0.07 (-0.11– -0.03)
$d = 0.5$ $\Gamma \in [23.4, 24.3]$	0.13 (0.09–0.17)	0.07 (0.03–0.11)	0.02 (-0.02–0.06)	-0.03 (-0.07–0.01)	-0.09 (-0.12– -0.05)	-0.14 (-0.17– -0.10)
$d = 0.6$ $\Gamma \in [\ .\ ]$	0.13 (0.09–0.17)	0.06 (0.03–0.10)	0.003 (-0.03–0.04)	-0.06 (-0.09– -0.02)	-0.12 (-0.15– -0.08)	-0.18 (-0.21– -0.14)

The differences $d = p_{01} - p_{00}$ and s= $p_{1\cdot} - p_{0\cdot}$ capture the outcome effect of *U* in the absence of treatment and the effect of *U* on the selection into treatment, respectively. *d* and *s* uniquely define the parameters p_{ij}, with $i, j \in \{0,1\}$. The simulated ATTs associated to the corresponding differences *d* (in rows) and *s* (in columns) are shown in each cell (95% Confidence Intervals in parentheses). Each ATT is averaged over 100 iterations. Γ denotes the average estimated odds ratio of *U* in the logit model of $\Pr(Y = 1|T = 0, U, W)$. Λ is the average estimated odds ratio of *U* in the logit model of $\Pr(T = 1, U, W)$. The baseline estimate without confounder is 0.151 (95% CI: 0.12–0.18).

Table D4. Sensitivity analysis of the propensity score for catastrophic expenditure: characterizing 'killer' confounders, Ghana 2012-2013

	$s = 0.1$ $\Lambda \in [1.4, 1.8]$	$s = 0.2$ $\Lambda \in [2.1, 2.7]$	$s = 0.3$ $\Lambda \in [3.2, 4.3]$	$s = 0.4$ $\Lambda \in [5.2, 9.6]$	$s = 0.5$ $\Lambda \in [9.8, 27.6]$	$s = 0.6$ $\Lambda \in [32.8, 40.1]$
d = 0.1 $\Gamma \in [1.5]$	-0.03 (-0.04 – -0.01)	-0.03 (-0.05 – -0.01)	-0.03 (-0.05 – -0.01)	-0.03 (-0.05 – -0.01)	-0.03 (-0.05 – -0.01)	-0.03 (-0.06 – -0.01)
d = 0.2 $\Gamma \in [2.2, 2.6]$	-0.03 (-0.04 – -0.01)	-0.03 (-0.05 – -0.02)	-0.03 (-0.05 – -0.02)	-0.04 (-0.05 – -0.02)	-0.04 (-0.06 – -0.02)	-0.04 (-0.06 – -0.02)
d = 0.3 $\Gamma \in [3.6, 3.7]$	-0.03 (-0.05 – -0.02)	-0.04 (-0.05 – -0.02)	-0.04 (-0.06 – -0.03)	-0.05 (-0.07 – -0.03)	-0.05 (-0.08 – -0.03)	-0.06 (-0.08 – -0.04)
d = 0.4 $\Gamma \in [6.9, 7.0]$	-0.04 (-0.05 – -0.02)	-0.04 (-0.06 – -0.03)	-0.05 (-0.07 – -0.04)	-0.06 (-0.08 – -0.04)	-0.07 (-0.09 – -0.05)	-0.08 (-0.11 – -0.06)
d = 0.5 $\Gamma \in [23.3, 23.7]$	-0.06 (-0.08 – -0.04)	-0.08 (-0.10 – -0.07)	-0.11 (-0.13 – -0.09)	-0.14 (-0.16 – -0.11)	-0.16 (-0.19 – -0.13)	-0.19 (-0.22 – -0.15)
d = 0.6 $\Gamma \in [\ .\ ]$	-0.17 (-0.18 – -0.15)	-0.26 (-0.28 – -0.24)	-0.35 (-0.37 – -0.33)	-0.45 (-0.47 – -0.42)	-0.54 (-0.57 – -0.51)	-0.63 (-0.67 – -0.60)

The differences $d = p_{01} - p_{00}$ and s= $p_{1\cdot} - p_{0\cdot}$ capture the outcome effect of U in the absence of treatment and the effect of U on the selection into treatment, respectively. d and s uniquely define the parameters p_{ij}, with $i, j \in \{0,1\}$. The simulated ATTs associated to the corresponding differences d (in rows) and s (in columns) are shown in each cell (95% Confidence Intervals in parentheses). Each ATT is averaged over 100 iterations. Γ denotes the average estimated odds ratio of U in the logit model of $\Pr(Y = 1|T = 0, U, W)$. Λ is the average estimated odds ratio of U in the logit model of $\Pr(T = 1, U, W)$. The baseline estimate without confounder is -0.02 (95% CI: -0.03 – -0.01).

Chapter 2

The speculum of marital age: How early marriage impacts women's use of opportunistic cervical and breast screening in India

Abstract

Background
The consequences of women's social status on health are widely discussed in the literature, yet partly owing to the difficulty in measuring the complex phenomenon of disempowerment, few have offered insight into how the conditions of social life affect women's health utilization. Our main objective is to investigate the effect of female empowerment, in the form of marital age, on women's use of cervical and breast screening in India, while exploring the channels that mediate and moderate the relationship.

Methods
We linked data from a sample of 15,903 ever-married women (15-49 years) who participated in the National Family Health Survey in 2015-16 with district-level data from the Indian Ministry of Health on per capita health facility supply. Drawing on Lauver's theory of care-seeking behaviour, we incorporate women's health insurance status into the analysis as a critical factor facilitating the external conditions that enable women to seek care. Our empirical strategy relies on a twofold instrumental variable approach seeking to generate quasi-random sources of variation in marital age and insurance participation. Specifically, we instrument age of first union by age of first menstruation and insurance status by cluster insurance rate in order to isolate their causal influence on women's health utilization. Using structural equation modelling, we test (i) whether financial self-efficacy mediates the relationship between marital age and opportunistic screening and (ii) to what extent the district-level per capita supply of community health centres (CHCs) moderates the strength of the mediating channel.

Results
The prevalence of ever having cervical and breast screening is 23 and 9 percent, respectively. We show that with every additional year that marriage is postponed, the probability of a woman ever having a cervical exam significantly increases by 7.9 percentage points and that of having a breast exam by 5.1. We find that higher marital age is associated with improvements in financial self-efficacy, which in turn, positively influence women's use of cervical and breast screening. This is an important finding as it reveals financial self-efficacy to be consistent with a 'second-stage' form of empowerment resulting from marriage postponement. We also show that the indirect effect of marital age on cervical screening mediated through financial self-efficacy is positive and significant for any value of district supply greater than 3.6 CHCs per million inhabitants. This points to the critical burden that a poor supply context may have on women's health utilization despite the relative improvements in autonomy associated with marital age.

Conclusion
Our findings suggest that losses in female empowerment attributed to early marriage partly explain Indian women's low cervical and breast screening participation. Interventions aiming to address the uniquely high prevalence of women's cancers in India would be wise to reflect on the health utilization consequences that can be attributed to socio-cultural practices exacerbating female disempowerment. Enforcing legal protections against underaged marriage is an actionable arena where both social and health agendas may converge in the interest of women – and good public policy.

1. Introduction

Marital age matters. Women who marry before the age of 18 tend to have more children, shorter birth intervals and more unintended pregnancies (1–3). Adolescent girls giving birth under the age of biological maturity are more likely to be undernourished, have higher maternal mortality and are remarkably susceptible to pregnancy-related morbidity (4–6). As the accruing evidence reveals that children born to adolescent women tend to have lower birth weight, higher infant mortality, increased risk of stunting and lower secondary school attainment, it has become clear that the health penalties of maternal underage marriage extend far into the progeny's life course (7,8). Whilst illuminating the relations between early marriage and detrimental health outcomes among young mothers and their children is worthwhile, much of the literature addressing marital age does so largely owing to its association with fertility and maternal childbearing age. Indeed, there are myriad psycho-social consequences of early marriage that may affect the ability of women – irrespective of motherhood status – to exercise informed choices and, thus matter for public health (9).

By accelerating the transition from childhood to womanhood, early marriage constrains girls to forgo critical opportunities to develop a sense of self-identity *vis-à-vis* a sense of place in society (10). In parallel, early marriage crucially affects women's human capital accumulation by disrupting educational attainment (11). In societies where marriage signals women to leave school in order to prioritize the domestic role encompassed in wife and home-maker, young married girls tend to forego the acquisition of necessary skills, thereby complicating labour market entry later in life (12,13). Moreover, in traditional South East Asian cultures, young married girls are likely to enter a joint family household environment, whereby they may experience control, and often violence (14,15), leading to an increased risk of depression and suicidality (16,17). Together, stunted psycho-social development, human capital disruption, domestic violence and detrimental mental health have implications on adult women's autonomy and agency. These outcomes limit the ability of young girls to exercise self-efficacy during a critically formative period, which may, in turn, condition them to accept and justify their own subordinated status in their households and communities well into adulthood.

The disempowerment of women attributed to early marriage conveys a key implication. Women who lack sovereignty over their own lives are ill-prepared to make decisions regarding their own health, as tiers of people intervene between their own perceptions of need and their actual decisions (15). Exposed to the relentless experience of powerlessness in the family sphere, child brides are more likely to become women with decreased autonomy in decision-making (18), and may thus develop a thwarted sense of self-efficacy, or personal competence to address a variety of demanding and novel situations (19). Moreover, in light of the association between self-efficacy and utilization of health services (20,21), we should expect that women for whom marriage precedes the age of maturity to have lower self-efficacy, as well as lower health utilization, particularly regarding services perceived as preventive or elective. The literature has thus far treated the inquiry on marital age and women's health utilization obliquely by focusing exclusively on maternal and child health.

Indeed, evidence shows that women who marry underaged are less likely to have a skilled health care professional present during delivery, have lower odds of attending antenatal and postnatal care visits and are less prone to give complete immunizations to their children (22–25). Paradoxically, the most serious lacuna in this literature is the absence of women-centered health utilization outcomes as they relate to marital age.

Though some women may be mothers, it is relevant that we distinguish between women's use of services throughout their lifecourse, heretofore women-centered health utilization, and women's use of services during pregnancy and childbirth, conventionally known as maternal health utilization. In underlining this distinction, it is salient that the utilization to which this literature has paid attention exclusively studies the punctual period in a woman's life when she may be pregnant, giving birth or caring for newborn children at the expense of every other moment in her lifecourse. This is puzzling considering that, in India, 200,000 more women die from breast and cervical cancer than from complications due to pregnancy and childbirth (26). As women's health includes yet extends far beyond maternal health, it is important that we explore women and their agency in the context of practices that precipitate female disempowerment if we are to understand, and as a public health project, influence the shape of, women-centered utilization of health services.

Research on gender differences in health utilization exposes systemic underutilization of services by women. Based on outpatient visits to a large public hospital in India, Kapoor et al. reveal an overall sex ratio of 1.7 male to one female visit, whereby 49% of the total outpatient visits made by women are missing (27). Several studies based on the Indian context show analogous findings. Ramakrishnan et al. find female gender significantly predicts non-compliance with surgery among children requiring corrective intervention for congenital heart disease (28). Not only are boys 3.5 times more likely to receive the life-saving procedure, but girls are less likely to receive it due to parents' apprehension that surgical scars may dampen marriage prospects. Likewise, Asfaw et al. show that being a girl significantly decreases the likelihood that Indian households will use expensive mechanisms to finance inpatient health care costs (29). Moreover, financially constrained households responding to health care shocks are more likely to favour boys than girls in their hospitalization decisions.

In highlighting the importance of accounting for the layers of barriers that women may face prior to accessing health services, the accruing literature calls for a deeper inquiry into the disempowering mechanisms that may discourage women to seek care. Our main contribution is to disentangle the complex interplay between female disempowerment, in the form of early marriage, and health utilization among women at risk of underaged marriage. We utilize nationally representative data from India to establish, for the first time, the effect of marital age on use of women-centered health services, namely cervical and breast screening, as well as on maternal health utilization. We incorporate women's health insurance status into the analysis as a critical factor facilitating the external conditions that enable women to seek care. We submit that while losses in agency attributed to young marital age may constitute intangible barriers to health service access among women exposed to underaged marriage

(24), inadequate or no insurance coverage constitutes a material barrier to service utilization among uninsured women (30–32). Thus, our analysis relies on a twofold instrumental variable approach seeking to generate quasi-random sources of variation in marital age and insurance participation. We employ empirical strategies proposed by Field and Ambrus (12) and Lu et al. (33), who instrument women's age at marriage by menarcheal age and insurance status by cluster insurance rate, respectively, in order to isolate their causal influence on women's health utilization.

Our second contribution is to unpack the channels which mediate and moderate the effect of early marriage on women's use of cervical and breast screening. First, we test whether women's financial self-efficacy mediates the relationship between marital age and opportunistic screening. This is an important focus of our work, as we hypothesize that financial self-efficacy is consistent with a form of female empowerment resulting from increased marital age. Second, we seek to explain whether and to what extent the supply of health facilities moderates the mediating channel between financial self-efficacy and use of screening among women. Drawing on Hayes (34), we test a moderated mediation hypothesis using structural equation modelling, thus revealing the direct and conditional indirect effects of marital age on cervical and breast screening, controlling for health insurance. Our paper is poised to reveal the causal effect of female empowerment on women-centered health utilization and bare the channels facilitating women's care-seeking behaviour. To this end, we proceed as follows. The remainder of this section offers a detailed account of the institutions underlying early marriage and health insurance in India, while the following section describes the data, identification strategy and statistical models. Lastly, Section 3 reports the study's findings, whose policy implications are discussed in Section 4.

1.1. Early marriage in India

Nearly half of the women in South Asia are married before their eighteenth birthday (35). Although India is not a signatory to the United Nations Convention on Consent to Marriage, Minimum Age for Marriage and Registration of Marriages, the government passed the Prohibition of Child Marriage Act in 2006, setting the minimum marital age at 18 years for girls and 21 for boys (36,37). Notwithstanding legal progress and owing to poor enforcement, the National Crime Records Bureau lists 395 reported cases in 2017, obfuscating the true extent of underage marriage in India (38). Indeed, according to the last decennial census of 2011, India is home to 223 million child brides, of whom 102 million were married before turning 15 (39). Deeply entrenched social customs practiced widely due to high social approval and religious resonance are critical factors driving India's high prevalence of child marriage. Extant practices like (i) sororate, where younger sisters marry their elder sisters' husbands if they fail to conceive, (ii) *mathamma*, where lower caste girls are married to village elders, (iii) *attasatta*, where girls are married in exchange for their brother's bride, and (iv) communal relationships, where young girls are married to repay debt or take a loan, highlight the extent to which women's low status determines and reproduces early marriage in Indian society (40).

1.2. Indian health insurance landscape

India's health insurance sector is characterized by fragmentation. The Employees' State Insurance Scheme (ESIS), the Central Government Health Scheme (CGHS), and *Rashtriya Swasthya Bima Yojana* (RSBY) are the most prominent pan-Indian insurance programmes (41). While ESIS offers comprehensive coverage to workers in the formal sector with monthly contributions equal to 1.75% of wages, CGHS extends a generous comprehensive medical care package to Central Government employees and pensioners with the payment of monthly salary-based contributions (42,43). Considering that 81% of India's workforce is composed of informal labourers lacking a secure source of income, most turn to RSBY, the largest central government scheme targeting informal workers below the poverty line (44,45). Covering 41 million families, RSBY offers an inpatient service package capped at INR 30,000 per household per annum with the payment of an annual premium (46). Moreover, Indian NGOs operate a patchwork of Community Health Insurance Schemes (CHIS) offering benefit packages that include inpatient, outpatient and diagnostic care with payment of an annual premium equivalent to an adult weekly wage (47–49). Although the variety of schemes available creates tiered coverage, we should expect health insurance to offer greater access to services, which may in turn expedite opportunistic screening and maternal care among insured women.

2. Methods

2.1. Sources of data

We use data from India's National Family Health Survey (NFHS-4). The details have been described elsewhere (50) but briefly, NFHS-4 is a nationwide representative household survey conducted in 2015-16 with technical assistance from the Demographic and Health Survey (DHS-VII) program. A two-stage stratified cluster sampling design makes the NFHS-4 representative at national, regional and district levels. In the first stage, 28,586 primary sampling units (*i.e.* clusters) were sampled across 36 states and union territories with weighted probabilities proportional to population size and sorted according to woman literacy rates. In the second stage, 22 households were randomly selected from each rural and urban cluster. Thus, covering a nationally representative sample of 601,509 households across 28,586 geographic clusters. This frame is used to identify 699,686 eligible household-dwelling women aged 15-49 years who participate in a woman-specific questionnaire aimed at gathering information on topics including marriage, reproductive behaviour, menstrual history, maternal and child health, health care utilization, women's empowerment and household gender relations.

To examine the effect of marital age on cervical and breast screening, we restricted the study sample to ever-married women between 15 and 49 years, who experienced menarche between the ages of 11 and 17, with non-missing values for marital age (n=15,265), whereas to study maternal care utilization, we further constrained the sample to women who had a birth in the 3 years preceding the interview (n=9,681). We use data from the Indian Ministry

of Health and Family Welfare (MoH), released under the National Data Sharing Accessibility Policy, pertaining to the district-wise availability of health centres in 2011 (51). This is ideal as the 2011 census enumeration areas constitute the sampling frame used for the selection of clusters in NFHS-4. Data on district population is extracted from 2011 Census Statistics (52) and matched to the MoH data on district-wise availability of health centres to compute per capita supply. We merged district-level MoH data on health facility supply per capita to individual-level NFHS-4 data to investigate the role of the supply context in the hypothesized relationship between marital age and opportunistic screening.

2.2. Variable description

Cervical and breast screening are our primary outcome measures. These are binary variables indicating whether a woman ever underwent an examination of the cervix or breasts, respectively. Considering that the location and form of the examination are not specified, it is plausible that women may have reported examinations conducted by medical professionals, as well as autonomously. Three binary maternal care utilization variables are our secondary outcome measures indicating (i) whether a woman who had a birth in the preceding three years had any prenatal care, (ii) had at least four antenatal care visits during pregnancy and (iii) whether the neonate received any postnatal care within two months of birth.

We use age of first union, a continuous variable, to define the age when a woman entered into an official marriage. Health insurance is a binary variable representing a woman's individual participation in an insurance program, where 1=insured and 0, otherwise. We measure the degree of women's financial self-efficacy with an index that includes variables on whether she: (i) has a functioning bank or savings account, (ii) has money that she can decide how to use independently, (iii) knows of any programs that give loans to women to start a business, and (iv) has ever taken a loan to start or expand a business. Women who respond affirmatively are coded as 1 and the variables are added to create the Financial Self-Efficacy index (FSE), whose scores range from 0 to 4. In the absence of a screening-specific self-efficacy scale, we assume that a woman's degree of confidence to engage in the steps necessary to make an independent decision regarding her financial wellbeing may approximate her confidence to make decisions regarding her general wellbeing (*e.g.* finding a health service provider, traveling to a health facility). Moreover, giving the association between general and task-specific self-efficacy scales (53), we are convinced that the FSE index used herein is an acceptable proxy measure for general self-efficacy. Finally, per capita health facility supply is measured using a continuous variable that expresses the number of community health centres (CHCs) available in the district where a woman resides for every 10,000 residents.

Age of menarche is an ordinal variable ranging from 7 to 17 years. Though recall accuracy is a reasonable concern, the timing of menarche has been shown to be reliable in numerous studies (54,55) giving the social importance attached to the onset of puberty. For instance, in India, when a Hindu girl reaches menarche, Ritushuddhi is the celebration of her rite of passage, which is marked by wearing a half-sari for the first time (56). Thus, it is reasonable

to expect that women living in traditional societies are more likely to remember menarcheal age with precision (12). Drawing from the literature, we construct a variable for cluster insurance rate that expresses insurance prevalence in the geographic cluster where a woman lives (33,57). Our data is composed of 28,586 clusters, each representing a demarcated geographic area consisting of 22 households. The insurance prevalence rate for an individual *i* living in cluster *k* equals the number of insured persons in cluster *k* minus the insurance status of the same individual divided by the total number of persons in the cluster (57).

2.3. Statistical models

We use OLS models to estimate the effect of marital age and health insurance on the probability that a woman uses screening and maternal care. Each model postulates that use of cervical (m_1) and breast screening (m_2), prenatal (m_3), antenatal (m_4) and postnatal (m_5) care are functions of age at first union ($c_1 Marital\ age_i$) and insurance status ($d_1 Insured_i$), in addition to sociodemographic, household and regional characteristics:

$$Y_{ihr}^{m_{1,2,3,4,5}} = \alpha_1 + c_1 Marital\ age_i + d_1 Insured_i + X_i'\beta_1 + W_{ih}'\delta_1 + Z_{ihr}'\zeta_1 + \varepsilon_{1ihr} \quad (1)$$

where individual-level (i) variables are represented by vector β, household-level (h) variables by vector δ and region-level (r) variables by vector ζ. Individual-level variables include age, number of children, employment status, education level, frequency of watching television and subjective degree of difficulty reaching medical help. Household-level variables include wealth index, religion, caste and rural residence. We include deciles of net state domestic product per capita to control for heterogeneity in capital stock across states and union territories.

2.4. Identification strategy

A key methodological challenge in our study requires tackling two endogeneity issues. On the one hand, it is difficult to assess the extent to which health care utilization outcomes among women are driven by the timing of marriage *vis-à-vis* prevalent factors linked to poverty and detrimental gender norms hindering women's autonomy. On the other hand, it is similarly challenging to assume that health insurance be uncorrelated with known determinants of health care use, including an *ex-ante* need for medical care. Thus, the present analysis relies on an instrumental variable approach that seeks to generate quasi-random sources of variation in insurance participation and marital age, independent from these endogeneity processes.

First, we employ age of menarche as an instrument to generate an exogenous source of variation in the timing of first union. Giving that, in India, marriage is aligned with durable social norms compelling families to protect the virginal status of future wives, the onset of puberty generates a strong incentive for parents to arrange their daughters' marriages (58). In particular, parents may perceive that, after menarche, unmarried daughters face a greater risk of engaging in sexual intercourse, which may in turn, result in worsened marriage prospects.

We can thereby expect marital age to be bounded below by natural variation in the timing of menarche, generating quasi-random differences in women's probability of early marriage (59). The assumption that marriage postponement is the only channel through which puberty onset influences adult women's decision to use health care services is reasonable. Indeed, evidence shows that genetic variation is the strongest predictor of the timing of first menses, pointing to a high degree of genetic determinism and a negligible role of environmental factors on the female pubertal process (60,61).

Second, we use cluster insurance rate to generate a quasi-random assignment in individual insurance status. The assumptions we make regarding the instrument's relevance and exclusion requirements are two-fold: (i) women who live in geographic clusters with high prevalence of insured individuals tend to be insured, and (ii) women's insurance status is the only pathway through which cluster insurance influences use of health services. We claim that a correlation between insurance status and cluster insurance is possible because: (i) clusters with high insurance prevalence may result when geographical areas share higher quality of health services, and (ii) women living in clusters with a higher concentration of insured residents are likely to observe and be influenced by the enrolment behaviour of their peers, which may positively determine their own participation in insurance (62). Thus, to the extent that women are embedded in social networks within geographical clusters, social learning is a conduit through which networks may shape participation in insurance, and ultimately increase the likelihood of insurance clusters.

We include age of menarche and cluster insurance rate in first-stage OLS-IV regressions and obtain the predicted probabilities of marital age (v_1) and insurance participation (v_2) for each woman:

$$X_{ihr}^{v_{1,2}} = \alpha_2 + c_2 menarche\ age_i + d_2 cluster\ rate_i + X_i'\beta_2 + W_{ih}'\delta_2 + Z_{ihr}'\zeta_2 + \varepsilon_{2ihr} \quad (2)$$

Predicted coefficients are used in second-stage regressions to estimate the causal effect of marital age and health insurance on each of five opportunistic screening and maternal utilization outcomes:

$$Y_{ihr}^{m_{1,2,3,4,5}} = \alpha_3 + c_3 \widehat{Marital\ age}_i + d_3 \widehat{Insured}_i + X_i'\beta_3 + W_{ih}'\delta_3 + Z_{ihr}'\zeta_3 + \varepsilon_{3ihr} \quad (3)$$

We performed Cragg-Donald Wald tests of endogeneity on the significance of the correlation coefficients between the errors of first- and those of second-stage equations under the null of exogeneity.

2.5. Structural equation modelling

While the effect of insurance on utilization of health services is widely recognized in the literature (30,33,57), the potential effect that marital age may exert on women-centered health utilization remains less straightforward. In light of this, we steer our analysis to unpack the channels which mediate and moderate the effect of early marriage on women's use of

cervical and breast screening. Specifically, we test whether women's financial self-efficacy mediates the relationship between marital age and opportunistic screening, conditioned on health facility supply. This is an important focus of our work, as we hypothesize that self-efficacy is consistent with a form of female empowerment resulting from increased marital age.

We elucidate the process through which marital age exerts an effect on cervical and breast screening using the predicted values of age at first union resulting from the first-stage IV regression to test our moderated mediation hypothesis. To this aim, we employ structural equation modelling (SEM) to simultaneously test (i) whether financial self-efficacy mediates the relationship between marital age and opportunistic screening and (ii) to what extent per capita CHC supply moderates the strength of the mediating channel. The following system of equations estimate our moderated mediation model:

$$FSE\ score\ (M) = \alpha_M + a\hat{X} + \varepsilon_M \tag{4}$$

$$Screening\ (Y^{m_{1,2}}) = \alpha_Y + c'\hat{X} + (b_1 + b_3 W)M + b_2 W + u_Y(\beta, \delta, \zeta) + \varepsilon_Y \tag{5}$$

where $\hat{X}$ represents the predicted values of marital age (instrumented by menarcheal age), M represents the financial self-efficacy mediator ($FSE\ score$), W represents the b-path moderator ($CHC\ supply$), MW represents the mediator-moderator interaction term ($FSE * CHC$), and Y the dependent variable for cervical (m_1) and breast (m_2) screening. In addition, the outcome equation includes vectors of individual- β_Y, household- δ_Y and state-level ζ_Y controls. Figure 1 depicts our moderated mediation path model in conceptual and statistical form.

We estimate the indirect effect of marital age on cervical screening through financial self-efficacy as the product of paths linking $\hat{X}$ to Y through M: (i) the $\hat{X} \rightarrow M$ path estimated as a in Equation (4) and (ii) the $M \rightarrow Y$ path estimated as $\theta_{M \rightarrow Y} = b_1 + b_3 W$ from Equation (5). We then estimate the conditional indirect effect ω of $\hat{X}$ on Y through M at levels of CHC supply (W):

$$\omega = a\theta_{M \rightarrow Y} = a(b_1 + b_3 W) \tag{6}$$

to examine how differences in marital age map onto differences in cervical screening, indirectly through financial self-efficacy and contingent on the value of per capita CHC supply. Finally, we use the index of moderated mediation, ab_3, which quantifies the rate of change of the indirect effect as CHC supply changes, as a formal test of moderated mediation (34). We compute effect sizes for direct (c') and indirect effects (ω) using MacKinnon's formula, which divides each by the total effect (63).

3. Results

Table 1 presents descriptive statistics. Mean marital age is slightly above 17 (ranging from 2 to 25), while mean menarcheal age is 13.5 years. Less than 14% of women participate in any

form of health insurance and less than 20% report being employed in the 12 months preceding the interview. Women in our sample are young, show wide variation in financial self-efficacy (FSE score: m=1.13; sd=0.99) and live in districts with substantially different supply of health facilities per capita (CHC: m=.05 per 10,000; sd=0.04). Figure 2 shows the district-level per capita CHC supply and financial self-efficacy score, highlighting districts above and below the mean. Over 20% of women report ever having cervical screening, whereas only 9% report ever having their breasts examined. In the subsample of women who had a birth in the preceding 3 years, 86% received some prenatal care, whilst slightly over 50% attended at least 4 antenatal care visits.

Figure 3 illustrates the mean ages at marriage corresponding to each year of menarche in the sample. Passed the age of 11, the timing of first marriage climbs steadily with the onset of puberty. Figure 4 shows the distributions of marital and menarcheal age among women who reached menarche between 7 and 17, revealing a symmetric shift in the timing of marriage with the onset of puberty. Over 30% of first marriages take place within 3 years of menarche. Less than 5% of women report prepubescent marriages, and in most cases (39%), marriage precedes menarche by 1 year. These patterns offer strong support for the assumption that earlier menarche is indeed associated with earlier marital age.

Though the medical literature suggests that variation in the timing of menarche is unrelated to external factors, some have highlighted the potential influence that acute spells of childhood malnutrition may have on menarcheal age (12). Giving that the extremely high levels of acute food restriction shown to postpone menarcheal age are fittingly critical as to be revealed in growth stunting, we examine whether the distributions of adult height change across menarche age. Figure 5, Panel A reveals that height distributions are similar across menarche subgroups. We check whether variation in the timing of first menses is due to geography and family background (Figure 5, Panels B and C) and show that menarche is uncorrelated with determinants of adult wellbeing, other than marital age, such that differences in environmental factors are unlikely to confound our analysis. We also check whether there are differences in the prevalence of adult health conditions across menarcheal age groups. Means in Table 2 reveal that observable measures of adult health outcomes are balanced across menarche age groups. Moreover, Figure 6 presents the proportion of women ever having screening by marital age, offering preliminary indication that marriage postponement is positively associated with both cervical and breast screening.

Table 3 presents the OLS-IV models for marital age, insurance and opportunistic screening. Results from the first-stage IV regressions are shown in Columns (1) and (2), offering evidence that age of menarche is strongly correlated with age at marriage and cluster insurance rate significantly predicts individual participation in health insurance. In particular, every additional year that puberty is delayed, marriage is postponed an estimated 0.12 year (p<0.001), while every unit-increase in the insurance prevalence rate of the geographic cluster where a woman lives, increases her probability of being insured by 75 percentage points (p<0.001). Thus, evidence accrued in the literature regarding the relationship between our instruments and their endogenous regressors is confirmed in our data (12,33,57–59).

Moreover, we conduct alternative first-stage specifications where various menarche age ranges are introduced as ordinal instrumental variables (not shown here), which confirm the direction and strength of the relationship between menarche and marital age. Reduced form coefficients for each outcome are shown in Columns (3) and (5). Complete first-stage OLS-IV regressions for women-centered health utilization outcomes are presented in Appendix A, Table A1.

Findings on the effect of marital age on cervical and breast screening are positive and significant. With every additional year that marriage is postponed, the probability of a woman ever having a cervical exam significantly increases by 7 percentage points and that of ever having a breast exam by 5. Of note, while health insurance positively and significantly predicts the likelihood that a woman receives cervical examination, we find no conclusive evidence that it affects the prospect of breast screening. This finding is meaningful, as breast screening can be performed both clinically and autonomously, and while insurance likely facilitates access to the former, it is irrelevant to the latter. Our interpretation is that a sufficient fraction of the breast screening reported consists of self-examinations, thus providing a reasonable basis for the negligible effect of health insurance. Table 4 presents the OLS-IV models for marital age, insurance and maternal care services. We consistently find that health insurance exerts positive, sizeable and significant effects on prenatal, antenatal and postnatal care. Per contra, we fail to detect a non-negligible effect of marital age on maternal health utilization. Complete first-stage OLS-IV regressions for maternal health utilization outcomes are presented in Appendix A, Table A2.

We proceed to investigate the extent to which marital age, instrumented by menarche onset, captures female empowerment. Table 5 presents estimated effects of marital age on cervical and breast screening conditioned on women's decision-making power in the household. Our results show that the positive and significant effect that marital age exerts on cervical and breast screening is captured among women who share decision-making power equitably with their partners. Moreover, when conditioning on tolerance towards wife beating, we observe the positive relationship between postponed marital age and opportunistic screening entirely among women who believe beating is unjustifiable intimate partner behaviour (Table 6). This suggests that the effect of marital age on cervical and breast screening, instrumented by menarche onset, reliably aligns with female empowerment.

We then examine whether financial self-efficacy acts as a potential mechanism through which marital age influences screening. Figure 7 presents estimated effects conditioned on dichotomous levels of the financial self-efficacy score. Though we find no conclusive indication that marital age affects screening exclusively through financial self-efficacy, the effect that marital age has on both cervical and breast screening is positive and significant among financially independent women. This reveals that the relationship between marital age and screening is partly mediated via the channel of financial self-efficacy.

Table 7 presents the moderated mediation coefficients and conditional effects of marital age and financial self-efficacy on cervical screening. We find that an increase in marital age

increases financial self-efficacy (a=0.149, p<0.001) and the probability of cervical screening directly (c'=0.056, p<0.05). Moreover, the effect of financial self-efficacy on cervical screening is indeed contingent on CHC supply, as evidenced by their statistically significant interaction (b_3=0.477, p<0.001). The sign of the interaction is consistent with the interpretation that the indirect effect of marital age on cervical screening through financial self-efficacy is larger for women living in districts with higher supply of CHCs. Figure 8, panel A, shows that, holding marital age constant, the conditional direct effect of financial self-efficacy on cervical screening ($\theta_{M\rightarrow Y}$) increases at each value of per capita CHC supply.

Figure 8, panel B, offers a visual representation of the moderation of the effect of financial self-efficacy on cervical screening by relevant values of CHC supply (mean, ±1SD). The relationship between financial self-efficacy and cervical screening is increasingly positive among women who live in districts with greater availability of CHCs per capita. Indeed, the direct effect of financial self-efficacy on cervical screening differs significantly between women who live in districts with average compared to high CHC supply (0.015 *vs* 0.038). Among women who live in districts with the lowest supply of CHCs (long-dashed line), we find no evidence that financial self-efficacy significantly affects the probability of cervical screening. Likewise, for women with least financial self-efficacy, we find no indication that getting a cervical exam differs substantially by CHC supply. Thus, suggesting that a threshold of per capita CHC supply exists, below which a woman's degree of financial self-efficacy, however high, no longer positively influences her ability to seek cervical examination.

Figure 8, panel C, presents the conditional indirect effect ($a\theta_{M\rightarrow Y}$) of marital age on cervical screening via financial self-efficacy at relevant values of CHC supply, plotted with a 95% confidence band. The index of moderated mediation represented by the slope of the line (ab_3), is the rate of change in the function linking the indirect effect to the moderator. The effect of marital age on cervical screening through financial self-efficacy is a significantly increasing function of CHC supply (0.071, p<0.001) (Table 7), hence the mediation is moderated. We probed the moderation of the indirect effect by identifying the value of CHC supply upon which the effect of marital age on cervical screening through financial self-efficacy transitions from statistically significant and not. The conditional indirect effect is positive and significant for any value of CHC supply greater than 0.036.

Combined, our findings suggest that while marital age exerts a substantial direct effect on cervical screening, 55% of the total effect occurs indirectly through financial self-efficacy conditional on per capita CHC supply (ω=0.069, p<0.001). For women living in poorly supplied districts, the effect is nullified irrespective of their degree of financial self-efficacy, whereas women living in well-supplied districts incur the benefits of increased marital age on cervical screening as CHC supply raises. This points to the critical burden that a poor supply context may have on women's care seeking behaviour *vis-à-vis* the relative improvements in autonomy associated with the increased financial self-efficacy that results from marriage postponement.

We replicated the moderated mediation model using supply of lower-level health facilities as alternative moderators, namely subcentres and primary health centres, conveying robustness of the conditional indirect effect estimates (not shown here). As it regards the second outcome variable, we find that an increase in marital age significantly increases the probability of breast screening (c'=0.047, p<0.01). While both the direct effect of financial self-efficacy on breast screening ($\theta_{M\rightarrow Y}$) and the indirect effect of marital age on breast screening through financial self-efficacy ($a\theta_{M\rightarrow Y}$) increase with higher values of CHC supply, we find no conclusive indication that the effects are significant (ab_3=0.019, p=0.059) (Appendix B: Moderated mediation analysis for breast screening).

4. Discussion

Our focus in investigating the causal links between women's empowerment, in the form of marriage postponement, health insurance and use of essential women-centered health services is driven to provide empirical support in designing relevant policy interventions. By instrumenting the individual decision to participate in health insurance with cluster insurance rate we isolated the causal effect of insurance on utilization in a subsample of women for whom it is more likely that peer-effects, and not *ex-ante* need for medical care, affected insurance status. In parallel, by instrumenting marital age with age of menarche we identified the causal effect of early marriage on health utilization in a subsample of women for whom random genetic variation in the onset of puberty, and not external factors, affected the timing of first union. To this end, our identification strategy is largely attributed to the preconditions that traditional marriage institutions impose on the bodies of women, thus capturing the effect that the detrimental status of women in Indian society may have on the use of health services. Indeed, if women's status does actually improve with marriage postponement – as suggested by both anthropological evidence and empirical findings (12,14,15) – our work advances the literature in finding that raising a woman's status by increasing marital age improves her use of health services, and thus matters for public health.

To the best of our knowledge, this is the first study that examines the causal effect of marital age on women's health utilization, revealing an important mechanism facilitating care-seeking behaviour among women at risk of underaged marriage. Our findings show that higher marital age significantly increases the likelihood that women attend cervical and breast examinations. Indeed, the effect that a one year-increase in marital age exerts on cervical screening is sizeable and commensurable to being enrolled in health insurance. While inadequate insurance coverage constitutes a well-known material challenge to health utilization, our findings show that losses in agency attributed to young marital age constitute a barrier of like magnitude to women's use of screening services. In parallel, we consistently find that health insurance predicts women's use of prenatal and postnatal care, while failing to detect a significant effect of marital age on any maternal utilization outcome. Although women exposed to underaged marriage are more likely to mother children within the narrow decisional boundaries established by their partners (15), our findings suggest that when holding health insurance constant, early marriers may nonetheless take effective steps to care

for their children in the gestational and postnatal period. Our second contribution to the literature stems from incorporating individual attributes, as well as characteristics of the health supply environment into a structural equation analysis that unpacks the underlying mechanisms. We reveal therewith, (i) that the effect of marital age on cervical screening is mediated by a woman's degree of self-efficacy and show (ii) that the mediating channel is contingent on the per capita supply of CHCs available in the district where a woman lives. Together, our findings indicate that while marital age exerts a substantial direct effect on cervical screening, 55% of the total effect occurs indirectly through this moderated mediation channel.

Specifically, our findings indicate that with every additional year that marriage is postponed, the probability of a woman having a cervical exam significantly increases by 7 percentage points and that of having a breast exam by 5. Our results pose a critical question – how does raising the status of women by increasing marital age improve the use of cervical and breast examinations? The prevailing qualitative literature offers at least three explanations that emphasize the conditions of women's social life as principal determinants of individual care-seeking behaviour. First, the alienation of women's bodies inherent in cultural practices that precipitate disempowerment render the female body and its functions impure, thereby proscribing women from learning to care for their own bodies, especially their reproductive organs (64). In India, the female body is perceived as *tīṭṭu* or polluting during menstruation and childbirth (65), which – in generating shame – obscures reproductive health knowledge and impedes women from recognizing symptoms of illness. Stigma associated with reproductive health issues lead to women being prohibited from coming forward for routine cervical and breast examinations (66,67). Moreover, the belief that female reproductive health problems are a reflection of poor character prevents even symptomatic women from seeking care (68).

Second, expectations placed upon women as caregivers often lead to the subordination of their own health needs and prevent them from incorporating routine medical check-ups into their health practices (69). In a study exploring breast cancer early detection among Indian women, Dey et al. show that ambivalence about prioritizing own health and tendency to bear pain avert women from using screening services (70). Echoing these findings, Pelcastre-Villafuerte et al. find that women's justification for neglecting early signs of cervical cancer is deeply sown to the belief that their responsibility towards family caretaking supersedes their own wellbeing (71). The authors also find fear of spousal abandonment in the aftermath of a diagnosis to be a paralyzing barrier to screening. Far from an isolated experience, others have exposed the extent to which spousal disapproval negatively influences screening attendance (69). A multi-country cervical screening study shows that 39% of women with precancerous lesions decline treatment fearing spousal dissent (72), while Wong and Kawamoto reveal that women forgo scheduled Pap smears because their spouses regard the examination as shameful (73). Indeed, seeking care for one's self is a subversive act in settings where the dominant cultural inscription upholds the impropriety of women who prioritize their own needs over the needs and wants of others.

Third, the detrimental psycho-social outcomes attributed to early marriage have long-term negative implications on decision-making autonomy, and ultimately on perceived self-efficacy (18,19), which in turn, influences care-seeking behaviour. Assessing the perceived benefits and barriers for cervical screening among Korean American women, Tung et al. show that women with lower self-efficacy are less likely to attend screening (74), while Hasnain et al., who examine Muslim women's participation in mammography screening in the U.S., find that self-efficacy is significant in distinguishing between women who had never had a mammogram and those who had at least one (75). In this regard, research suggests that a woman's degree of global confidence and optimistic belief in her own ability to produce a desired effect and lead a more active and self-determined life is a significant antecedent of care-seeking behaviour. Thus, bodily alienation, self-subordination and stunted self-efficacy should be borne in mind as some of the channels through which women may internalize stigmatizing social norms. Though our work explores self-efficacy as the mediating channel between marital age and screening utilization, it rests on the assumption that we offer but part of the explanation as to why women exposed to early marriage are less inclined to seek care.

We find that increasing marital age is associated with improvements in self-efficacy, which in turn, positively influence women's use of cervical and breast screening services. This is an important finding as it reveals self-efficacy to be consistent with a 'second-stage' form of female empowerment resulting from marriage postponement. Moreover, we test a moderated mediation hypothesis and show that the effect of self-efficacy on cervical screening is contingent on the district-level supply of health facilities. As such, the indirect effect of marital age on cervical screening mediated through self-efficacy is larger for women living in districts with higher per capita supply of CHCs. Furthermore, we show that the conditional indirect effect of marital age on cervical screening through the mediating channel of self-efficacy is positive and significant for any value of supply greater than 3.6 CHCs per million inhabitants. Women living in well-supplied districts incur the benefits of increased marital age on cervical screening through self-efficacy as CHC supply raises. In contrast, the indirect effect is nullified when women live in poorly supplied districts, irrespective of their degree of self-efficacy. Likewise, for women with least self-efficacy, we find no indication that getting a cervical exam differs significantly by CHC supply. This suggests that neither the self-efficacy mediating channel, nor the health facility supply moderating condition are sufficient to enable women to engage in care-seeking behaviour – instead, each is necessary.

The consequences of women's social status on health are widely discussed in the literature, yet partly owing to the difficulty in measuring the complex phenomenon of disempowerment, few have offered causal insight into how the conditions of social life affect women's health utilization. By exploiting natural variation in the timing of first menstruation, we use marital age itself as a speculum – a tool for improving observation in the interest of understanding the health-related consequences of an overt form of disempowerment. Our approach, however, is not without objection. The genetic component of menarcheal age, which we exploit in our analysis, may entail that women with delayed pubertal onset have the added social advantage of having mothers for whom marriage was also postponed. If this were true,

the benefits of later marriage would be attributed to intergenerational linkages and not biology (12). We sought to address this concern by comparing observable measures of family background characteristics, showing that these do not differ across menarcheal age groups. Moreover, others have shown that the impact of delaying marriage varies across marriage markets (76). In contexts where women's higher marital age is considered undesirable, dowries are often used as pecuniary transfers to compensate for a potentially 'lower' value of older women in the marriage market. However, due to lack of data on dowry, we could not explore the potential costs of higher marital age, nor the extent to which these could reasonably offset improvements in autonomy.

Owing to the woefully low prevalence of opportunistic screening among women, the most common and fatal sites of cancer in India are the cervix and the breasts (77). Indeed, up to 89% of Indian women diagnosed with cervical and breast cancers have metastatic disease at the time of presentation (78,79). Our research shows that losses in female empowerment attributed to early marriage partly explain Indian women's low screening participation. The policy conclusions derived from our analysis are clear. Elevating the status of women by implementing the existing legal protections against underaged marriage is critical to improve the use of cervical and breast screening. Moreover, female empowerment does not operate in a vacuum but requires the facilitating condition of an optimal health facility supply environment in order to promote screening participation. This points to the critical burden that a poor supply context may have on women's prevention seeking behaviour despite the relative improvements in autonomy associated with marital age and increased self-efficacy. As India implements its first National Cancer Screening Programme, policy-makers must address the disparities in screening uptake that emerge from the unequal geographic distribution of health facilities by offering tailored incentives to women who live in poorly supplied areas. Interventions aiming to address the uniquely high prevalence of women's cancers in India would be wise to reflect on the health utilization consequences that can be attributed to socio-cultural practices exacerbating female disempowerment. Enforcing legal protections against underaged marriage is an actionable arena where both social and health agendas may converge and flourish in the interest of women – and good public policy.

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Table 1. Descriptive statistics, India 2015-16

	N	Mean	SD	Min	Max
Women-centered health utilization					
Ever had a cervical exam	15,265	0.23	0.42	0	1
Ever had a breast exam	15,265	0.09	0.29	0	1
Maternal health utilization					
Any prenatal care	9,681	0.86	0.35	0	1
At least 4 antenatal care visits	9,612	0.50	0.50	0	1
Any postnatal care	9,666	0.37	0.48	0	1
Demographics					
Age	15,265	21.41	2.10	15	25
Marital age	15,265	17.84	2.58	2	25
Menarche age	15,265	13.54	1.16	7	17
Education (in years)	15,265	7.52	4.61	0	20
Insured	15,265	0.14	0.34	0	1
Employed	15,265	0.19	0.39	0	1
Number of children	15,265	1.07	1.01	0	9
Rural residence	15,265	0.78	0.42	0	1
Belongs to a scheduled caste/tribe	15,265	0.83	0.38	0	1
Household wealth index					
Poorest	15,265	0.21	0.41	0	1
Poorer	15,265	0.25	0.43	0	1
Middle	15,265	0.23	0.42	0	1
Richer	15,265	0.18	0.38	0	1
Richest	15,265	0.13	0.34	0	1
Religion					
Hindu	15,265	0.80	0.40	0	1
Muslim	15,265	0.12	0.33	0	1
Christian	15,265	0.05	0.21	0	1
Sikh	15,265	0.01	0.11	0	1
Other	15,265	0.02	0.14	0	1
Financial self-efficacy					
Financial self-efficacy index	15,265	1.13	0.99	0	4
Has bank/savings account	15,265	0.41	0.49	0	1
Has money and can decide its use	15,265	0.35	0.48	0	1
Knows where to take business loan	15,265	0.34	0.47	0	1
Has taken business loan	15,265	0.03	0.18	0	1
District-level supply of health facilities					
Subcentres per 10,000 inh.	14,860	1.44	0.70	0.004	11.41
Primary health centres per 10,000 inh.	14,861	0.24	0.19	0.007	5.07
Community health centres per 10,000 inh.	14,518	0.05	0.04	0.002	0.95

Table 2. Adult health outcomes by age of menarche groups, India 2015-16

	Menarche age				
	(1)	(2)	(3)		
	7-13 years	14 years	15-17 years	$t_{\Delta 1,2}$	$t_{\Delta 1,3}$
STIs	0.024	0.022	0.025	0.547	-0.355
Genital soars	0.030	0.025	0.031	1.664	-0.118
Genital discharge	0.093	0.088	0.106	0.942	-1.954
Anaemia	0.558	0.564	0.549	-0.640	0.877
High blood pressure	0.066	0.060	0.070	1.265	-0.651
Diabetes	0.004	0.005	0.004	-0.985	-0.436
Asthma	0.009	0.005	0.007	2.266*	0.870
Thyroid disorder	0.008	0.006	0.010	1.625	-0.913
Heart disease	0.005	0.005	0.006	0.312	-0.570
Cancer	0.001	0.000	0.001	0.793	0.081
Observations	7,696	4,835	2,734		

***p<0.001 **p<0.01 *p<0.05. Note: T-statistics report two-tailed equality of means tests between menarche group pairs. STIs: Sexually transmitted infections. Respondents report whether they currently have these health conditions. For STIs, genital soars and genital discharge, respondents report incidence in the 12 months preceding the interview.

Table 3. Marital age and women's use of cervical and breast screening services, India 2015-16

	First-stage		Cervical screening		Breast screening	
	(1)	(2)	(3)	(4)	(5)	(6)
	Marital age	Insurance	RF	OLS-IV	RF	OLS-IV
Age of menarche	0.122***		0.008**		0.006**	
	(0.016)		(0.003)		(0.002)	
Cluster insurance		0.750***	0.052**		-0.014	
		(0.015)	(0.016)		(0.011)	
Marital age				0.069**		0.053**
				(0.026)		(0.019)
Insurance				0.067**		-0.021
				(0.023)		(0.016)
Number of children				0.055***		0.042***
				(0.015)		(0.011)
Employment				0.030*		0.018*
				(0.012)		(0.009)
Constant	10.810***	-0.042	-0.185***	-0.931**	-0.141***	-0.712**
	(0.251)	(0.033)	(0.046)	(0.324)	(0.033)	(0.231)
CDW F-statistic				28.391		28.391
Observations	15,265	15,265	15,265	15,265	15,265	15,265

***p<0.001 **p<0.01 *p<0.05. Note: Robust standard errors in parentheses. RF: Reduced form regression; CDW: Cragg-Donald Wald. Controls include age, wealth, religion, caste, education, frequency of watching TV, rural residence, difficulty reaching nearest health facility and per capita state domestic product.

Table 4. Marital age and women's use of maternal health care services, India 2015-16

	Prenatal care			Antenatal care			Postnatal care		
	(1) Marital age	(2) Insurance	(3) OLS-IV	(4) Marital age	(5) Insurance	(6) OLS-IV	(7) Marital age	(8) Insurance	(9) OLS-IV
Age of menarche	0.117***			0.122***			0.116***		
	(0.019)			(0.019)			(0.019)		
Cluster insurance		0.737***			0.738***			0.736***	
		(0.019)			(0.019)			(0.019)	
Marital age			-0.001			0.034			0.056
			(0.025)			(0.034)			(0.039)
Insurance			0.131***			0.206***			0.210***
			(0.019)			(0.031)			(0.033)
Constant	13.921***	-0.032	0.702	13.849***	-0.032	-0.316	13.923***	-0.030	-0.642
	(0.284)	(0.040)	(0.391)	(0.283)	(0.041)	(0.531)	(0.284)	(0.040)	(0.605)
CDW F-statistic			19.104			20.993			18.851
Observations	9,681	9,681	9,681	9,612	9,612	9,612	9,666	9,666	9,666

****p<0.001 **p<0.01 *p<0.05. Note: Robust standard errors in parentheses. CDW: Cragg-Donald Wald. Controls include age, wealth, religion, caste, education, employment status, number of children, frequency of watching TV, rural residence, difficulty reaching nearest health facility and per capita state domestic product.

Table 5. Marital age, household decision making and use of preventive screening services, India 2015-16

	Cervical exam			Breast exam		
	(1)	(2)	(3)	(4)	(5)	(6)
Decision by:	Partner alone	Woman alone	Jointly	Partner alone	Woman alone	Jointly
Household purchases	0.009	0.267	0.103**	0.017	0.107	0.081**
	(0.045)	(0.375)	(0.035)	(0.032)	(0.199)	(0.025)
	4,717	652	8,914	4,717	652	8,914
Family/friend visits	0.033	-0.103	0.097**	0.022	-0.085	0.069**
	(0.045)	(0.611)	(0.032)	(0.030)	(0.462)	(0.023)
	4,499	710	9,189	4,499	710	9,189
Own health care	0.050	0.073	0.082**	0.010	0.346	0.058**
	(0.053)	(0.244)	(0.030)	(0.036)	(0.454)	(0.021)
	4,289	1,139	9,016	4,289	1,139	9,016

***p<0.001 **p<0.01 *p<0.05. Note: In each cell, the estimated effect and sample size are presented first and last, respectively. Robust standard errors in parentheses.

Table 6. Marital age, tolerance to wife beating and use of preventive screening services, India 2015-16

	Cervical exam	Breast exam
Wife beating justified	0.027	-0.001
	(0.028)	(0.020)
	6,168	6,168
Wife beating not justified	0.122*	0.128**
	(0.056)	(0.046)
	8,809	8,809

***p<0.001 **p<0.01 *p<0.05. Note: In each cell, the estimated effect and sample size are presented first and last, respectively. Robust standard errors in parentheses.

Table 7. Moderated mediation coefficients and conditional effects of marital age and financial self-efficacy on cervical screening, India 2015-16

		FSE score			Cervical screening	
		Coefficient	SE		Coefficient	SE
Marital age	a	0.149***	0.007	c'	0.056*	0.025
FSE score		−	−	b_1	-0.010	0.006
CHC per 10,000		−	−	b_2	-0.578***	0.160
FSE x CHC		−	−	b_3	0.477***	0.093
Constant		-1.523***	0.118		-0.759*	0.305
Total effect				c	0.125***	0.028
Indirect effect				ω	0.069***	0.013
IMM				ab_3	0.071***	0.014

Conditional effects at CHC per 10,000 = *mean and ±1SD*

	Direct effects $(\theta_{M\rightarrow Y})$		Indirect effects $(\omega = a\theta_{M\rightarrow Y})$	
CHC per 10,000	$\hat{b}_1 + \hat{b}_3 W$	SE	$\hat{a}(\hat{b}_1 + \hat{b}_3 W)$	SE
0.006	-0.008	0.006	-0.0012	0.0008
0.054	0.015***	0.004	0.0022***	0.0005
0.102	0.038***	0.006	0.0057***	0.0009

***p<0.001 **p<0.01 *p<0.05. Note: FSE: Financial self-efficacy index. IMM: Index of moderated mediation.

Figure 1. Conceptual and statistical representation of the moderated mediation model, India 2015-16

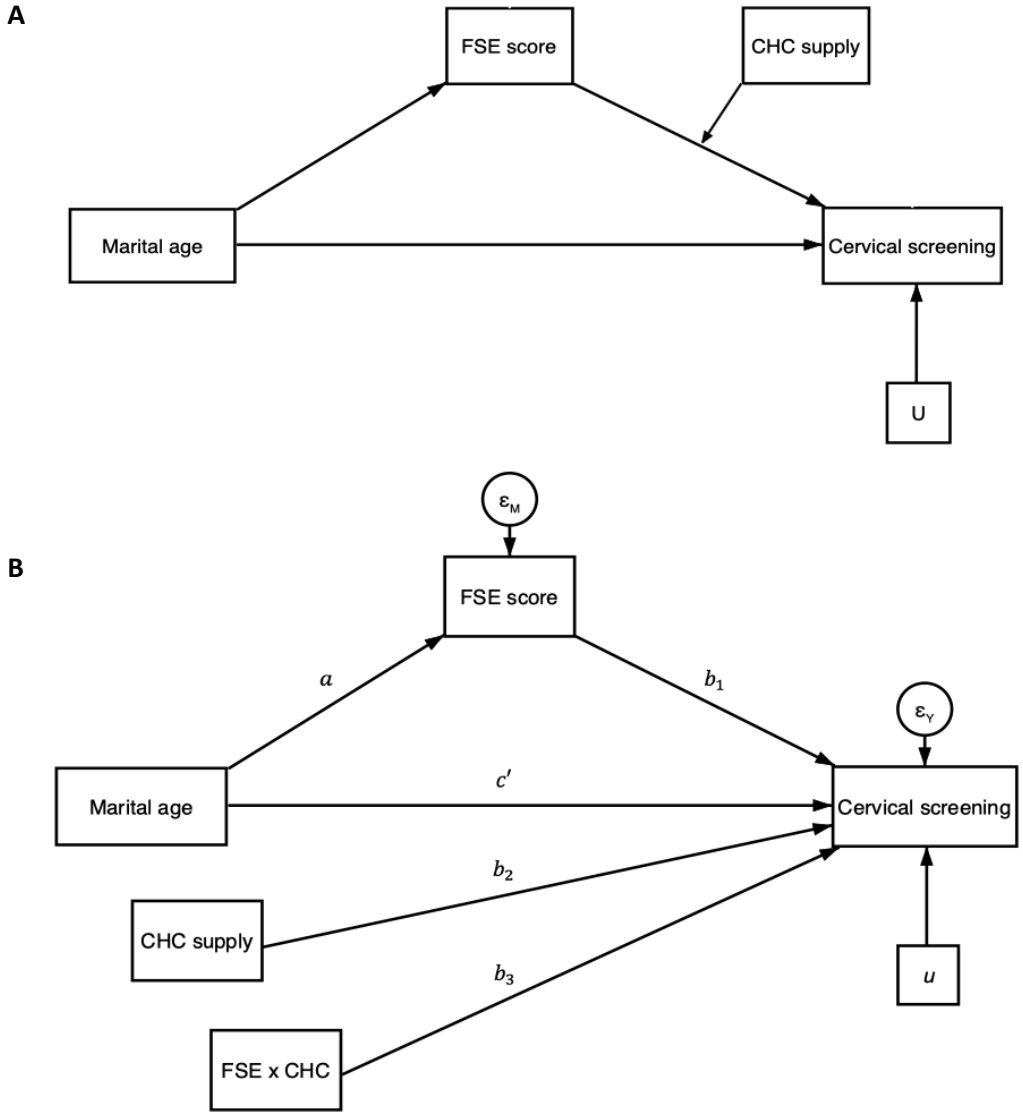
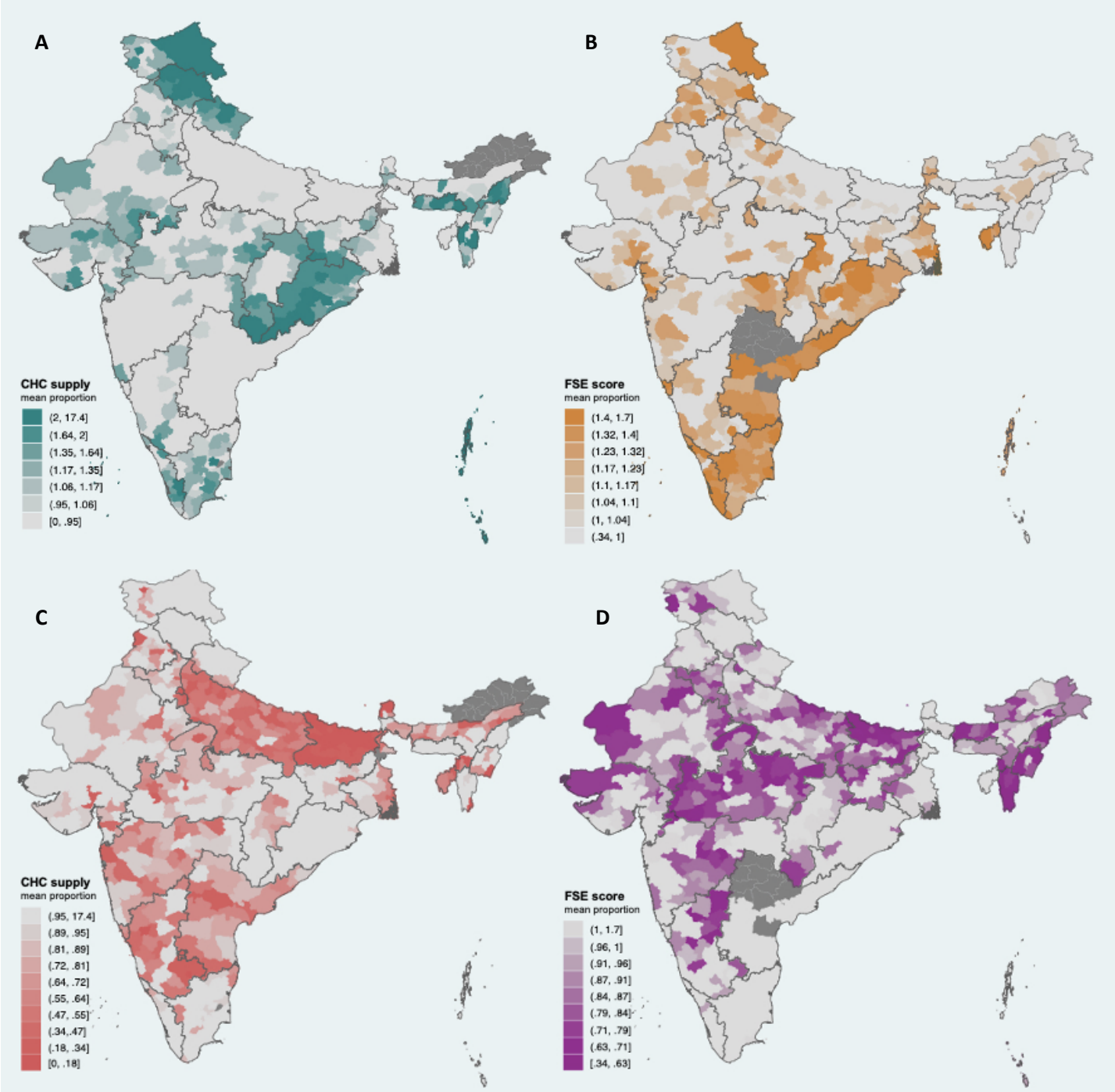


Figure 2. District-level per capita CHC supply and financial self-efficacy score, India 2015-16



Panels A and B present mean proportions above the mean for CHC supply and FSE score, respectively. Panels C and D present mean proportions below the mean.

Figure 3. Relationship between age of menarche onset and age at marriage, India 2015-16

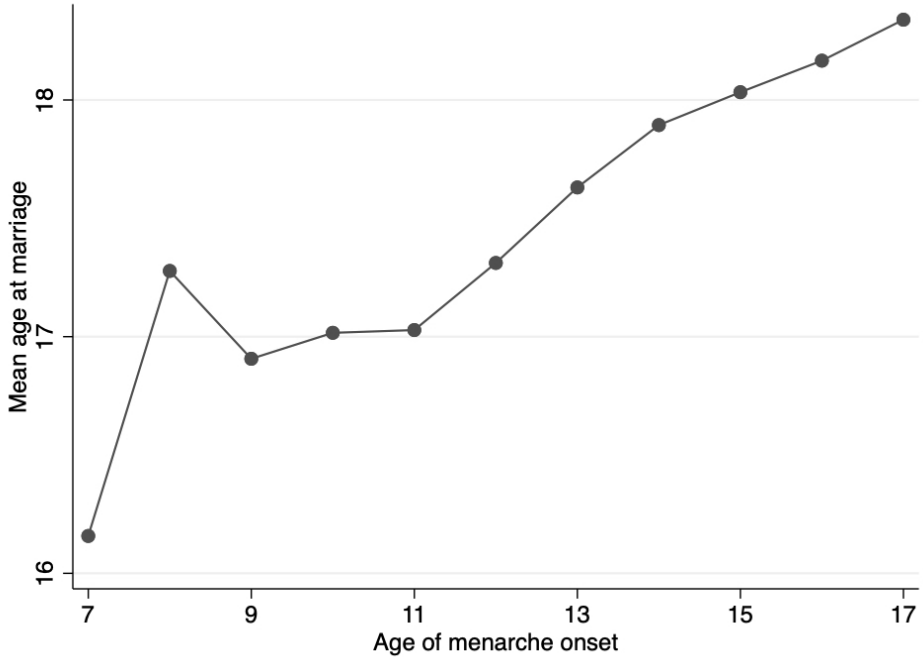


Figure 4. Distribution of age of menarche and age at marriage, India 2015-16

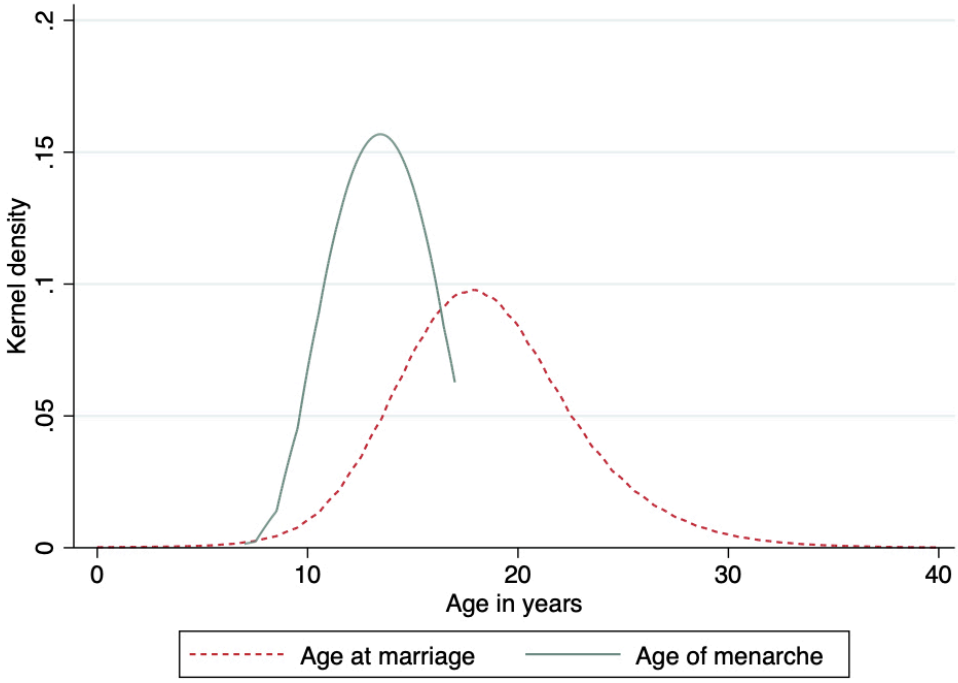


Figure 5. Distribution of height, geographic altitude and family wealth by menarche age, India 2015-16

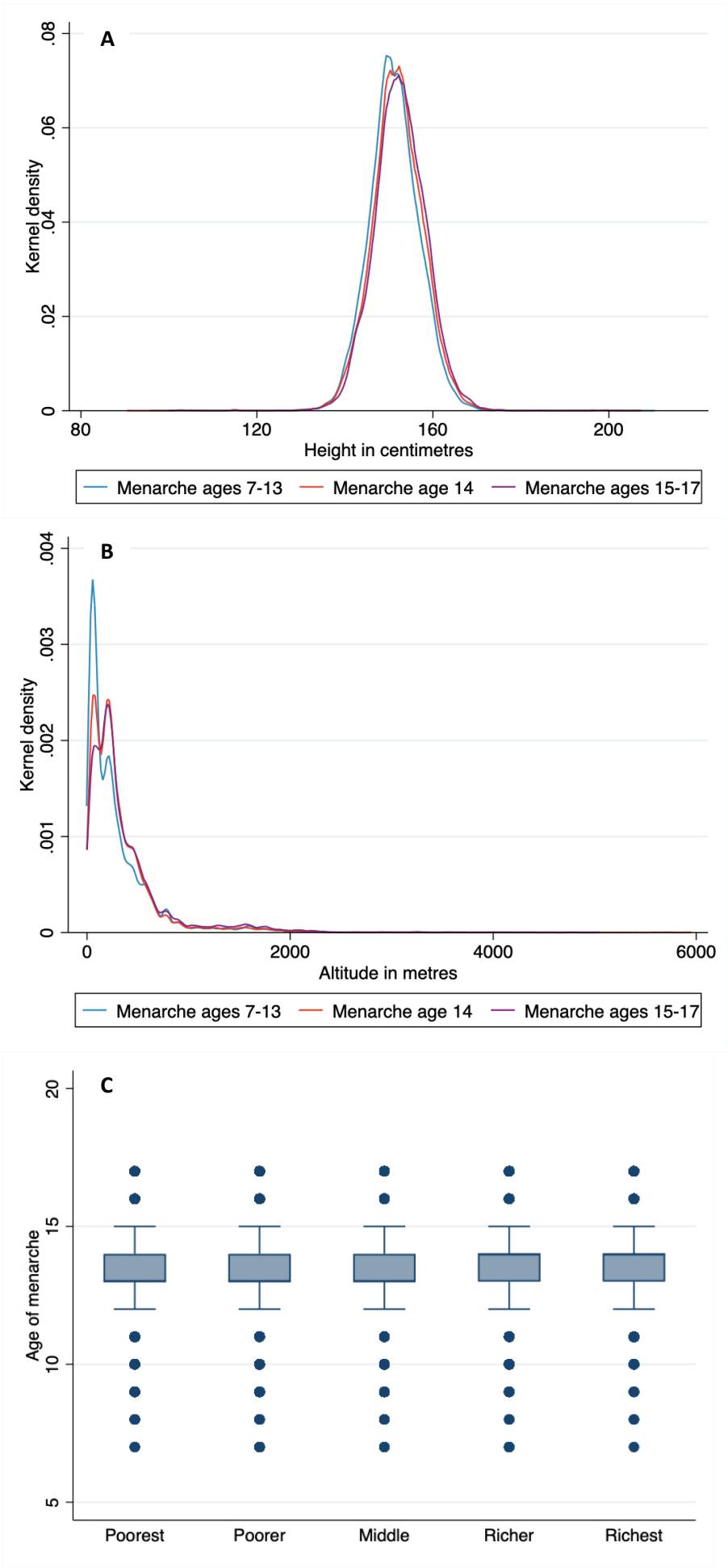


Figure 6. Cervical and breast screening by age at marriage, India 2015-16

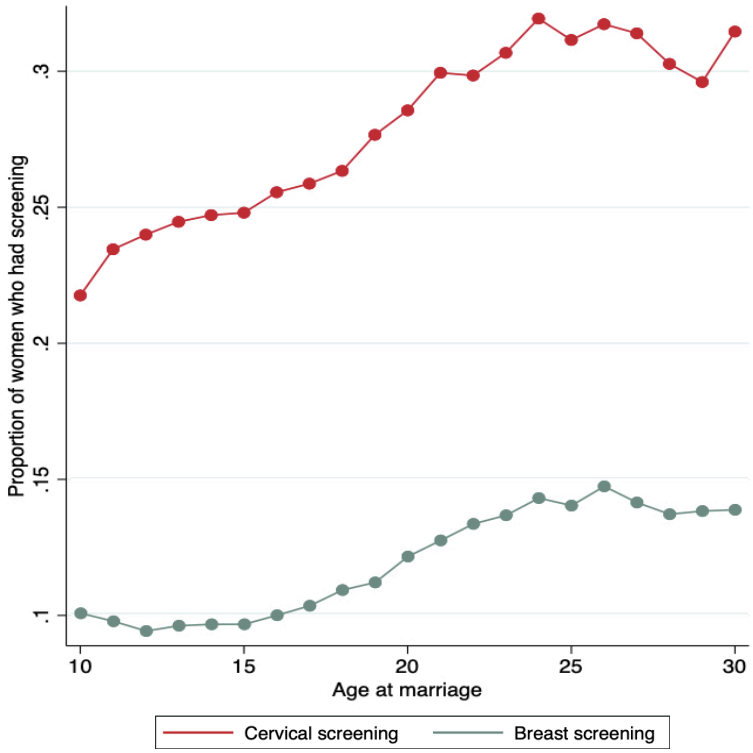


Figure 7. Effect of marital age on cervical and breast screening conditioned by levels of financial self-efficacy, India 2015-16

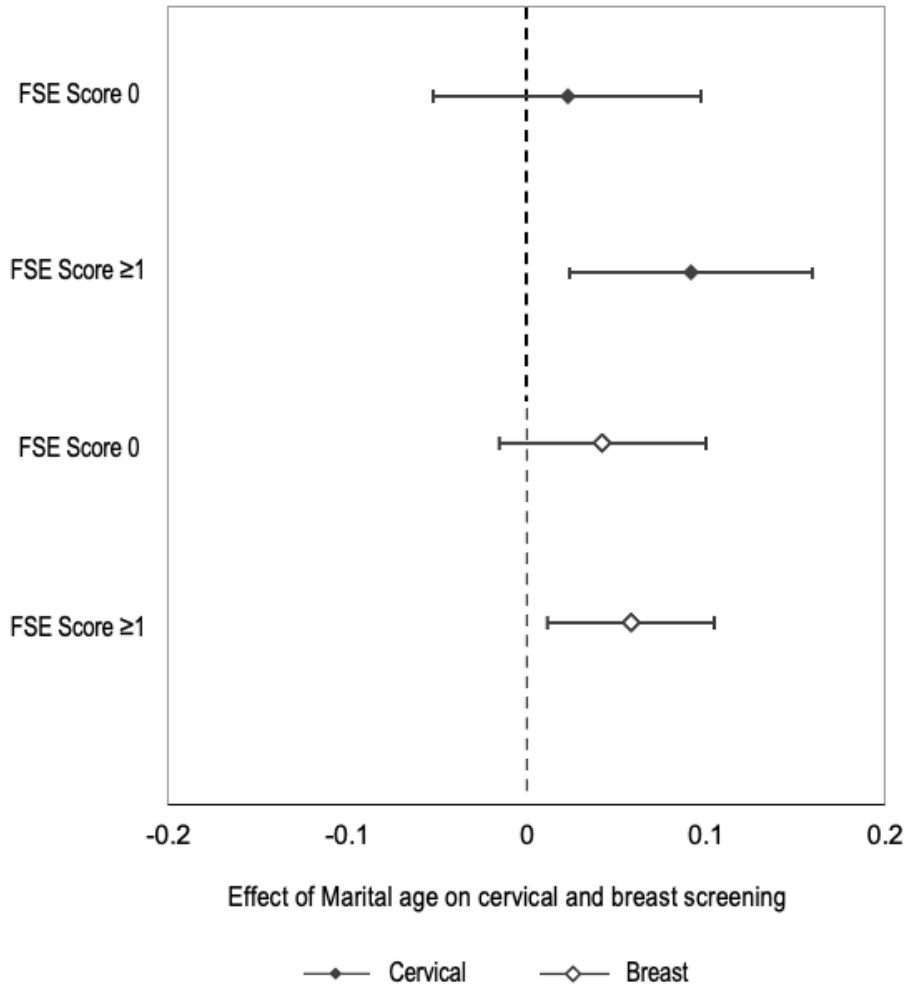
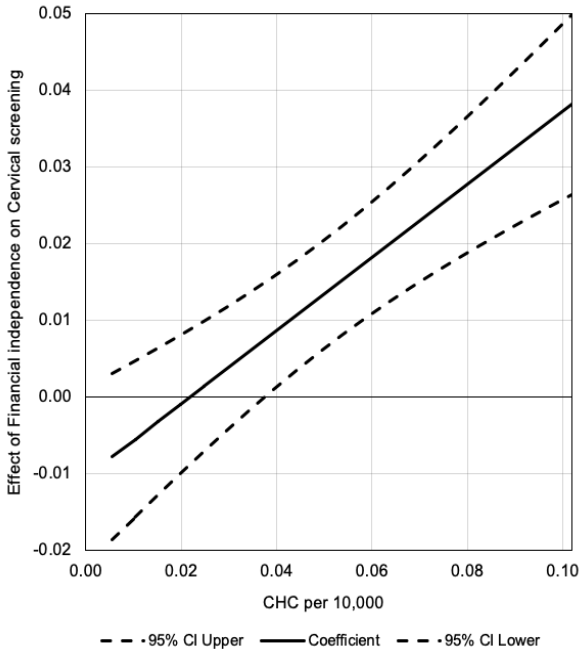
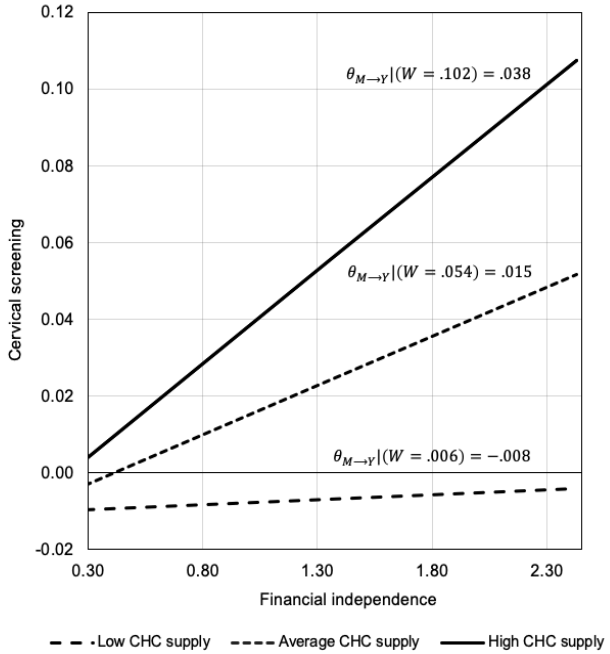
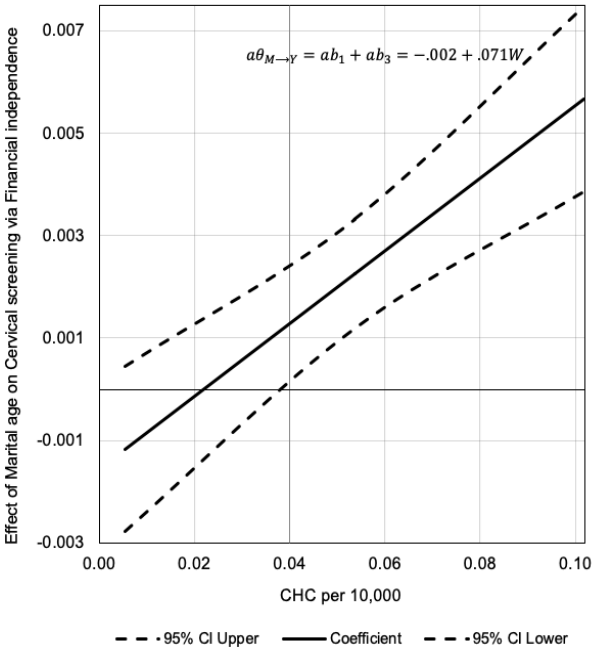


Figure 8. Conditional effect of marital age on cervical screening through financial self-efficacy at levels of per capita CHC supply, India 2015-16







Appendix A: First-stage IV regressions

Table A1. First-stage OLS-IV regressions for use of preventive screening services, India 2015-16

	Cervical screening		Breast screening	
	(1) Marital age	(2) Insurance	(3) Marital age	(4) Insurance
Age of menarche	0.122***	-0.001	0.122***	-0.001
	(.016)	(0.002)	(0.016)	(0.002)
Cluster insurance rate	0.031	0.750***	0.031	0.750***
	(0.082)	(0.015)	(0.082)	(0.015)
Age	2.119***	-0.004	2.119***	-0.004
	(0.046)	(0.006)	(0.046)	(0.006)
Number of children	-0.546***	0.004*	-0.546***	0.004
	(0.020)	(0.002)	(0.020)	(0.002)
Employed	-0.311***	0.019**	-0.311***	0.019**
	(0.050)	(0.007)	(0.050)	(0.007)
Secondary education	0.679***	0.006	0.679***	0.006
	(0.046)	(0.005)	(0.046)	(0.005)
Household wealth	0.362***	0.003	0.362***	0.003
	(0.019)	(0.002)	(0.019)	(0.002)
Religion	0.102***	0.007*	0.102***	0.007*
	(0.024)	(0.003)	(0.024)	(0.003)
Scheduled caste/tribe	-0.022	0.018**	-0.022	0.018**
	(0.050)	(0.006)	(0.050)	(0.006)
TV watching frequency	0.019	0.009	0.019	0.009
	(0.048)	(0.006)	(0.048)	(0.006)
Rural residence	0.031	0.002	0.031	0.002
	(0.048)	(0.006)	(0.048)	(0.006)
Difficulty reaching health facility	-0.005	0.002	-0.005	0.002
	(0.024)	(0.003)	(0.024)	(0.003)
Per capita state domestic product	-0.024***	0.001	-0.024***	0.001
	(0.007)	(0.001)	(0.007)	(0.001)
Constant	10.810***	-0.042	10.810***	-0.042
	(0.251)	(0.033)	(0.251)	(0.033)
CDW F-statistic	28.391	28.391	28.391	28.391
Observations	15265	15265	15265	15265

***p<0.001 **p<0.01 *p<0.05. Note: Robust standard errors in parentheses. CDW: Cragg-Donald Wald.

Table A2. First-stage OLS-IV regressions for use of maternal health services, India 2015-16

	Prenatal care		Antenatal care		Postnatal care	
	(1)	(2)	(3)	(4)	(5)	(6)
	Marital age	Insurance	Marital age	Insurance	Marital age	Insurance
Age of menarche	0.117***	-0.002	0.122***	-0.002	0.116***	-0.002
	(0.019)	(0.003)	(0.019)	(0.003)	(0.019)	(0.003)
Cluster insurance rate	0.069	0.737***	0.042	0.738***	0.065	0.736***
	(0.099)	(0.019)	(0.099)	(0.019)	(0.099)	(0.019)
Age						
15-19	Reference					
20-24	1.961***	-0.000	1.963***	-0.001	1.961***	0.000
	(0.059)	(0.010)	(0.059)	(0.010)	(0.059)	(0.010)
25-29	3.621***	-0.013	3.553***	-0.008	3.620***	-0.012
	(0.265)	(0.035)	(0.267)	(0.035)	(0.265)	(0.035)
Number of children	-0.387***	0.006	-0.390***	0.006*	-0.386***	0.006
	(0.025)	(0.003)	(0.025)	(0.003)	(0.025)	(0.003)
Employed	-0.258***	0.021*	-0.255***	0.021*	-0.257***	0.022*
	(0.057)	(0.009)	(0.057)	(0.009)	(0.057)	(0.009)
Secondary education	0.637***	0.013	0.643***	0.013	0.635***	0.014
	(0.052)	(0.007)	(0.052)	(0.007)	(0.052)	(0.007)
Household wealth						
Poorest	Reference					
Poorer	0.185***	0.003	0.177**	0.003	0.185***	0.003
	(0.067)	(0.009)	(0.066)	(0.009)	(0.067)	(0.009)
Middle	0.493***	0.007	0.476***	0.008	0.497***	0.007
	(0.076)	(0.010)	(0.075)	(0.010)	(0.076)	(0.010)
Richer	0.745***	0.018	0.729***	0.019	0.742***	0.018
	(0.087)	(0.012)	(0.086)	(0.012)	(0.087)	(0.012)
Richest	1.230***	0.027*	1.211***	0.028*	1.231***	0.028*
	(0.097)	(0.014)	(0.097)	(0.014)	(0.098)	(0.014)
Religion						
Hindu	Reference					
Muslim	0.129	0.003	0.128	0.004	0.133	0.003
	(0.069)	(0.008)	(0.068)	(0.008)	(0.069)	(0.008)
Christian	0.462***	0.015	0.458***	0.014	0.458***	0.013
	(0.102)	(0.017)	(0.102)	(0.017)	(0.102)	(0.017)
Sikh	1.171***	-0.057*	1.158***	-0.058*	1.173***	-0.057*
	(0.192)	(0.028)	(0.192)	(0.028)	(0.192)	(0.028)

Table A2. (continued)

	Prenatal care		Antenatal care		Postnatal care	
	(1)	(2)	(3)	(4)	(5)	(6)
	Marital age	Insurance	Marital age	Insurance	Marital age	Insurance
Other	0.076	0.004	0.067	0.011	0.076	0.004
	(0.157)	(0.023)	(0.158)	(0.022)	(0.157)	(0.023)
Scheduled caste/tribe	0.061	0.015*	0.052	0.016*	0.064	0.015*
	(0.059)	(0.007)	(0.059)	(0.007)	(0.059)	(0.007)
TV watching frequency	0.057	0.004	0.066	0.004	0.059	0.004
	(0.056)	(0.008)	(0.055)	(0.008)	(0.056)	(0.008)
Rural residence	-0.043	0.013	-0.041	0.012	-0.038	0.013
	(0.055)	(0.008)	(0.055)	(0.008)	(0.055)	(0.008)
Difficulty reaching health facility						
Distance is not an obstacle			Reference			
Distance is moderate obstacle	-0.071	0.004	-0.059	0.004	-0.071	0.004
	(0.052)	(0.007)	(0.052)	(0.008)	(0.052)	(0.007)
Distance is severe obstacle	0.026	0.009	0.027	0.010	0.024	0.009
	(0.055)	(0.008)	(0.055)	(0.008)	(0.055)	(0.008)
Per capita state domestic product						
Decile 1			Reference			
Decile 3	-0.141*	0.001	-0.154*	0.001	-0.139*	0.001
	(0.069)	(0.007)	(0.069)	(0.007)	(0.069)	(0.007)
Decile 4	-0.181	-0.013	-0.152	-0.013	-0.182	-0.013
	(0.113)	(0.012)	(0.109)	(0.012)	(0.113)	(0.012)
Decile 5	0.166*	-0.019	0.169*	-0.021	0.165	-0.019
	(0.084)	(0.012)	(0.085)	(0.012)	(0.084)	(0.012)
Decile 6	0.015	0.029**	0.017	0.030**	0.016	0.029**
	(0.081)	(0.011)	(0.081)	(0.011)	(0.081)	(0.011)
Decile 7	-0.435***	0.042*	-0.415***	0.042*	-0.437***	0.041*
	(0.120)	(0.021)	(0.120)	(0.021)	(0.120)	(0.021)
Decile 8	0.138	0.001	0.156	0.001	0.139	0.000
	(0.085)	(0.014)	(0.085)	(0.014)	(0.085)	(0.013)
Decile 9	-0.239**	0.012	-0.239***	0.011	-0.239**	0.012
	(0.081)	(0.011)	(0.081)	(0.011)	(0.081)	(0.011)
Decile 10	0.046	0.019	0.041	0.017	0.052	0.019
	(0.099)	(0.011)	(0.099)	(0.011)	(0.098)	(0.011)
Constant	13.921***	-0.032	13.849***	-0.032	13.923***	-0.030
	(0.284)	(0.040)	(0.283)	(0.041)	(0.284)	(0.040)

Table A2. (continued)

	Prenatal care		Antenatal care		Postnatal care	
	(1)	(2)	(3)	(4)	(5)	(6)
	Marital age	Insurance	Marital age	Insurance	Marital age	Insurance
CDW F-statistic	19.104	19.104	20.993	20.993	18.851	18.851
Observations	9681	9681	9612	9612	9666	9666

***p<0.001 **p<0.01 *p<0.05. Note: Robust standard errors in parentheses. CDW: Cragg-Donald Wald. No observations in our sample belong to Decile 2 of per capita state domestic product.

Appendix B: Moderated mediation analysis for breast screening

Table B1. Moderated mediation coefficients and conditional effects of marital age and financial self-efficacy on breast screening, India 2015-16

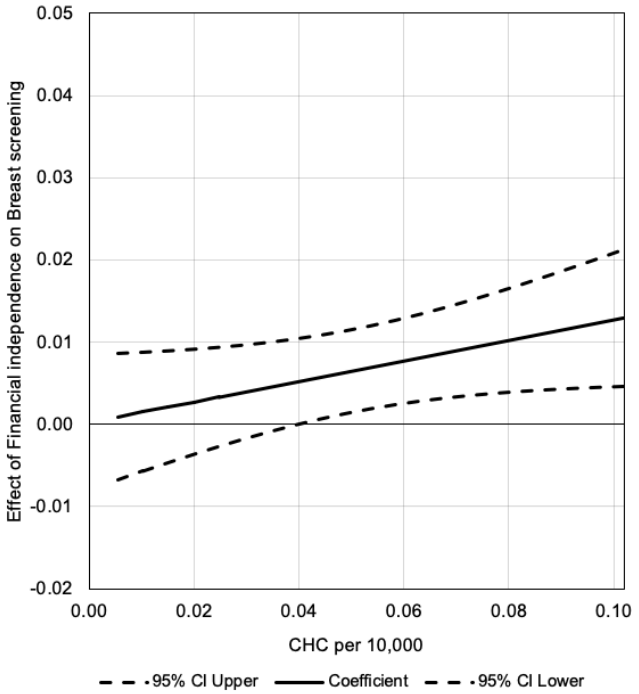
		FSE score			Breast screening	
		Coefficient	SE		Coefficient	SE
Marital age	a	.149***	.007	c'	.047**	.017
FSE score		−	−	b_1	.0002	.004
CHC per 10,000		−	−	b_2	-.178	.113
FSE x CHC		−	−	b_3	.125[b]	.066
Constant		-1.523***	.118		-.633**	.216
Total effect				c	.065**	.020
Indirect effect				ω	.019*	.009
IMM				ab_3	.019[b]	.010

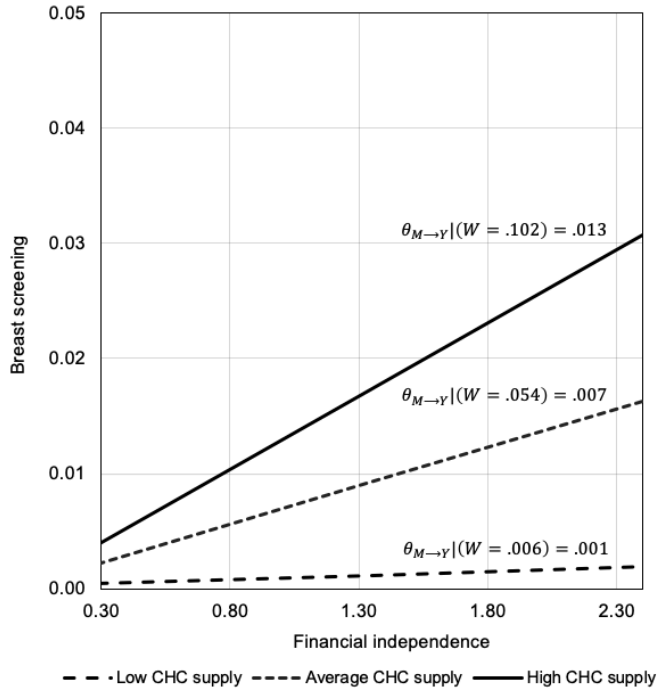
Conditional effects at CHC per 10,000 = *mean and ±1SD*

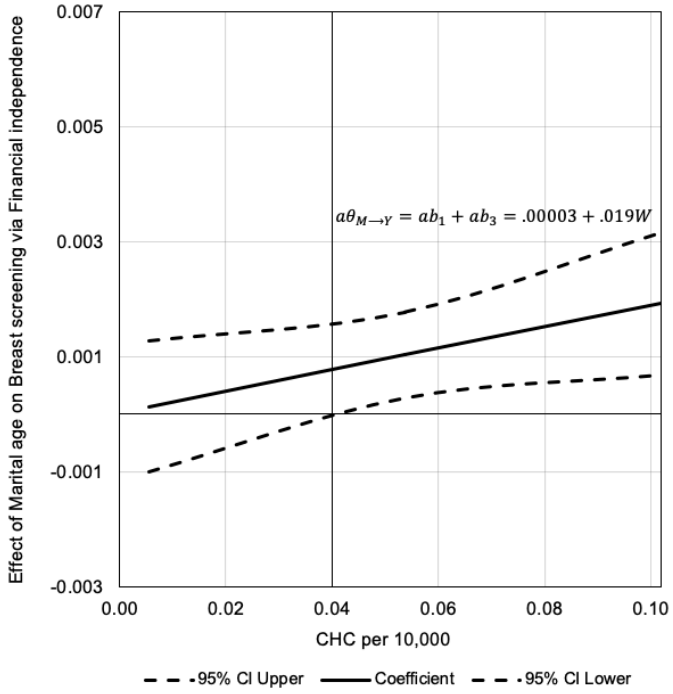
	Direct effects $(\theta_{M\rightarrow Y})$		Indirect effects $(\omega = a\theta_{M\rightarrow Y})$	
CHC per 10,000	$\hat{b}_1 + \hat{b}_3 W$	SE	$\hat{a}(\hat{b}_1 + \hat{b}_3 W)$	SE
.006	.001	.004	.0001	.0005
.054	.007**	.003	.0010**	.0004
.102	.013**	.004	.0019**	.0006

***p<0.001 **p<0.01 *p<0.05 [b]p<0.06. Note: FSE: Financial self-efficacy index. IMM: Index of moderated mediation.

Figure B1. Moderated mediation and conditional effects of marital age and financial self-efficacy on breast screening, India 2015-16







Chapter 3

Life-time smoking exposure, smoking-related fear of health consequences and thought given to screening among high-risk current and prior smokers attending a free LDCT lung cancer screening in Italy: a mediation analysis

Abstract

Background
Encouraging evidence from the NELSON and the National Lung Screening Trials reveals substantial mortality reductions in prior and current heavy smokers at high risk that can be attributed to screening with low-dose computed tomography (LDCT). While LDCT screening is now a fully integrated evidence-based procedure in the U.S. Medicare, European countries are gathering evidence that may lead to the adoption of mass lung cancer screening programs at national policy levels. However, low participation from higher risk groups threatens the effectiveness and sustainability of future national screening programs.

Methods
Aiming to contribute a better understanding of screening utilization among hard-to-reach groups, we investigate associations between life-time smoking exposure, smoking-related fear of health consequences and thought given to screening in a sample of current and prior heavy smokers who attended the first province-wide lung cancer screening program in Lombardy, Italy (2018-19) (n=1,112). We use structural equation modelling to test (i) whether the hypothesized adverse effect of life-time smoking exposure on thought given to screening can be explained by its association to smoking-related fear of health consequences and (iii) to what extent the mediated effect differs across socio-demographic groups. As the main predictor variable, we assess life-time smoking exposure by computing a comprehensive smoking index that incorporates smoking duration, intensity and time since cessation in a single aggregate measure.

Results
We find that life-time smoking exposure is negatively associated with extent of thought given to lung cancer screening ($c' = -0.32;\ p = 0.006$). This result supports our first hypothesis, namely that current and prior smokers with higher risk profiles tend to contemplate lung cancer screening less. To test our second hypothesis, we examine whether smoking-related fear of health consequences mediates the relationship between smoking history and thought given to screening. We find support for this prediction. Life-time smoking exposure predicts greater smoking-related fear of health consequences ($a = 0.17;\ p = 0.021$), which, in turn, predicts greater thought given to lung cancer screening ($b = 0.34;\ p < 0.0001$). Our findings reveal that the mediated channel significantly changes the sign of the relationship, suggesting that the mediator is protective ($ab = 0.06;\ p = 0.03$). Yet, for some groups – namely, individuals who are younger, women, higher educated and with better perceived physical health – we fail to detect a significant association between smoking history and smoking-related fear of health consequences. As such, in groups for whom the (protective) partially mediated channel is non-significant, the total effect of life-time smoking exposure on thought given to screening is more negative.

Conclusion
We find that nearly a fourth of the adverse effect of smoking history on thought given to screening could be mediated through its effect on fear of smoking-related health consequences. Considering this underlying mediational process, interventions aimed at cultivating interest in screening among high risk groups might benefit from invitation strategies that communicate the health benefits of participation whilst inspiring blame-free reflection.

1. Introduction

With an astounding 2.1 million new cases and 1.8 deaths in 2018 (1), lung cancer is the foremost cause of cancer mortality worldwide (2). In Europe alone, lung cancer results in the loss of nearly 3.2 million disability-adjusted life years annually (3). Though early detection is the strongest predictor of survival (4), most cases present at advanced stages and the minority of pre-clinical diagnoses tend to occur incidentally (5). Owing to this, lung cancer survival is lower than that of any other common malignancies (2). Against the foreground of typically bleak prognosis and infrequent early diagnosis, research attention is honed in on the potential risk reducing benefits of lung cancer screening. Indeed, the U.S. National Lung Screening Trial (NLST) offers convincing evidence that annual low-dose computed tomography (LDCT) screening effectively reduces the relative risk of lung cancer mortality by 20% (6). Echoing these findings, thoracic LDCT screening for active or prior heavy smokers at high risk of lung cancer is now an evidence-based, Medicare-covered test (7) recommended by the U.S. Preventive Services Task Force (8). In parallel, European mortality data has recently become available from the NELSON randomized controlled trial, revealing LDCT screening to be associated with lung cancer mortality reductions of 26% in men and 39-61% in women (9). These developments motivate European countries to review evidence leading to the adoption of lung cancer screening programs at national policy levels, with a focus on guidelines for its effective and safe implementation.

Achieving a positive benefit-harm ratio is central to the effectiveness and long-term sustainability of any national lung cancer screening program, which, in turn, depends upon uptake by those at high risk (10). This is echoed loudly by the fact that the majority of deaths averted in the NLST are attributed to participants within the three highest risk quintiles (11). Indeed, the sensitivity and positive predictive value of screening increases as programs are able to attract and engage individuals with higher risk profiles, thereby reducing avoidable invasive follow-up tests while lowering the number-needed-to-screen (12). Though the criteria for identifying high-risk individuals – mainly based on age, time since cessation, smoking duration and intensity – are clearly outlined (6); smoking history, the strongest predictor of increased risk (13), tends to predict lower screening attendance across European and U.S. trials (14–16). Research shows that, partly due to the stigma surrounding lung cancer as well as the fatalistic beliefs associated with a lung cancer diagnosis (17), ever smokers often prefer not to know (18). Indeed, the high-risk population that lung cancer screening programs hope to engage differs from those targeted for other types of screening in one important respect – smokers, who battle a nicotine addiction, often experience blame related to the perceived self-infliction of tobacco-related diseases secondary to lifestyle choices (19). As uniquely relevant to lung cancer, perceived stigma and blame may explain why high-risk individuals remain least likely to participate in screening.

Drawing from the Transtheoretical model (TTM), we submit that high risk individuals who attend lung cancer screening progress through a series of stages of readiness, which ultimately result in adopting the preventative behaviour: (i) precontemplation, knowledge of but no intention to attend screening, (ii) contemplation, serious thoughts about completing

screening, (iii) preparation, intention to complete screening and (iv) action, attending screening (20). In this model, contemplation, or thought given to screening, is a pivotal and necessary antecedent to screening attendance (21). Although the TTM is widely used in screening participation studies (22–25), the current state of the science in this specific cancer screening area is predominantly descriptive, qualitative research (26,27). Previous studies offer valuable insight into smokers' interest, perspectives and attitudes towards lung cancer screening (28), while others have shown that fear of diagnosis, as well as that of radiation exposure play a potent role as barriers (29). However, there is poor understanding about how smoking-related factors, such as history and fear of health consequences, might affect the extent to which smokers think about screening. This is relevant as we posit that the level of contemplation afforded to screening may distinguish high risk individuals who attend screening incidentally from those who attend with amplified internal motivators for behaviour change.

Aiming to address this gap, we use data from high risk individuals who attended the first free LDCT lung cancer screening program in Italy at the Humanitas Research Hospital to explore the effect of life-time smoking exposure on extent of thought given to screening. Ours is the first study to date that systematically investigates to what extent the association between smoking history and thought given to screening is mediated by smoking-related fear of health consequences. By elucidating the underlying mediational processes from life-time smoking exposure to thought given to screening, we may identify intervention targets relevant to high risk individuals, which, in turn, could mitigate the low screening attendance associated with smoking history. Hence, in the present study, we aim to explore (i) whether some of the hypothesized adverse effect of life-time smoking exposure on thought given to screening can be explained by its association with smoking-related fear of health consequences and (iii) to what extent the mediated effect differs across socio-demographic groups. By linking key smoking-related factors to the extent of thought that high-risk populations give to the screening procedure, we seek to contribute to the wider screening participation literature.

2. Methods

2.1. Data and variables

All patients included in this prospective analysis participated in the Smokers' Health Multiple Actions (SMAC) program, an ongoing free LDCT lung cancer screening program targeting current smokers with a smoking duration greater than 30 years, as well as prior heavy smokers older than 55 years. This high-risk sample (n=1,112) attended screening at the Humanitas Research Hospital in Milan, Italy, in the period between September 2018 and September 2019. This study was granted ethical approval by the General Directorate of Health and Biomedical Research Ethics Committee of the Italian Ministry of Health. All patients included in the study gave written informed consent and completed our questionnaire prior to screening. To examine the effect of life-time smoking exposure on extent of thought given to screening, we restricted the study sample to high-risk individuals with non-missing values across relevant variables (n=883).

Thought given to screening is our primary outcome measure, an ordinal variable indicating respondents' agreement with the statement "Screening is on my mind continually". We measure agreement on a 5-point Likert scale, ranging from 1 "strongly disagree" to 5 "strongly agree". As the main predictor variable, we assess life-time smoking exposure by computing a comprehensive smoking index (CSI) (30), which incorporates duration(dur), intensity(int) and time since cessation(tsc) in a single aggregate measure:

$$CSI = \left(1 - 0.5^{dur/\tau}\right)\left(0.5^{tsc/\tau}\right)\ln(int + 1). \quad (1)$$

Smoking intensity regards the number of cigarettes smoked per day and is log-transformed as studies (31) have shown intensity, but not duration, to have a significant non-linear effect on the logit of lung cancer risk. τ is the biological half-life parameter, representing the time required for a quantity of tobacco smoke-related carcinogens to reduce to half of its initial value in the body. A lower τ implies a faster levelling off of the impact of increasing both duration and time since cessation. In our study, we fixed the value of τ *a priori* to 25, following Leffondré et al.'s best parametrization (30), which assumes, for instance, that 20 years of cessation brings down the risk from 25.5 years of smoking to 12.4 years. The CSI equals zero for never smokers and increases with greater smoking history.

Finally, we assess the smoking-related fear of health consequences (SRFHC), our mediating variable, with a 4-item index measuring the respondent's degree of (i) fear, (ii) worry, (iii) anxiety and (iii) reflection experienced when thinking about the health consequences of smoking in the four weeks preceding the screening. Values of the SRFHC index range between 4 and 28, whereby higher scores indicate greater fear, worry, anxiety and reflection afforded to the health consequences of smoking behaviour.

2.2. Statistical models

We use structural equation modelling (SEM) to assess associations and statistical mediations among life-time smoking exposure, smoking-related fear of health consequences and thought given to lung cancer screening. The following system of equations estimate our mediation model:

$$SRFHC\ (M) = \alpha_M + aX + u_M + \varepsilon_M \quad (2)$$

$$Thought\ given\ to\ LCS\ (Y) = \alpha_Y + c'X + bM + u_Y + \varepsilon_Y \quad (3)$$

where X represents the continuous smoking history predictor variable, M represents terciles of SRFHC index and Y the ordinal dependent variable for thought given to lung cancer screening. We estimate the indirect effect of life-time smoking exposure on thought given to screening through smoking-related fear of health consequences as the product of the $X \rightarrow M$ path estimated as a in (2) and the $M \rightarrow Y$ path estimated as b in (3). c' estimates the direct effect of X on Y, holding M constant. The total effect of life-time smoking exposure on

thought given to screening is the sum of direct and indirect effect ($c' + ab$). Mediation occurs when the indirect effect is significant.

We compute the indirect effect size using MacKinnon's formula for calculating the mediated percentage, which is the indirect effect divided by the total effect (32). Structural equations for each endogenous variable in the pathway model are adjusted for the potential confounding effects of individual-level variables represented by u_M and u_Y. These include age, gender, education, body mass index, perceived physical health, measured as the raw physical score of the 12-item short-form health survey (SF-12), as well as personal and family tumor history. We conduct the mediation analysis in maximum likelihood and test the proposed model coefficients with 1,000 bootstrap iterations. Figure 1 depicts our model in statistical form.

3. Results

Table 1 presents demographic, smoking history, quality of life and clinical characteristics for the full sample, as well as across relevant groups of the mediator and outcome variables. The average age of respondents in our sample is 64 years, nearly 37% are women and most participants did not complete secondary schooling (64%). The mean CSI score (2.02) indicates that our sample is composed of heavy current and prior smokers at high risk. Of note, lung tumors are diagnosed in 11% of respondents, while other lung conditions, including chronic obstructive pulmonary disease, emphysema and chronic bronchitis are diagnosed in 33%.

Table 2 shows the main findings of the proposed mediation model, yielding good overall model fit ($R^2 = 0.14$). We find that life-time smoking exposure is negatively associated with extent of thought given to lung cancer screening ($c' = -0.32;\ p = 0.006$). This result supports our first hypothesis, namely that current and prior smokers with higher risk profiles (*i.e.* greater smoking duration and intensity but shorter time since cessation) tend to contemplate lung cancer screening less, compared to those with lower risk profiles. To test our second hypothesis, we examine whether smoking-related fear of health consequences mediates the relationship between smoking history and thought given to screening. We find support for this prediction. Life-time smoking exposure predicts greater smoking-related fear of health consequences ($a = 0.17;\ p = 0.021$), which, in turn, predicts greater thought given to lung cancer screening ($b = 0.34;\ p < 0.0001$).

Moreover, we reveal that 21% of the total effect of life-time smoking exposure on thought given to screening is mediated by smoking-related fear of health consequences ($ab = 0.06;\ p = 0.03$). Falling in the upper middle range on the basis of Cohen's guidelines (33), the indirect effect size is substantial. Our findings indicate that the partially mediated channel significantly changes the sign of the relationship – thereby suggesting that the mediator is protective. We may, thus, infer that when smoking history leads to greater fear of

smoking-related health consequences, smokers with higher risk profiles tend to contemplate lung cancer screening more.

Table 3 shows the mediated effect of life-time smoking exposure on thought given to screening across age, gender, education and perceived physical health groups. We consistently find that greater lifetime smoking exposure is negatively associated with extent of thought given to screening (c') – confirming that, irrespective of socio-demographic and perceived health characteristics, higher risk individuals contemplate screening less. Yet, for some groups – namely, individuals who are younger, women, higher educated and with better perceived physical health – we fail to detect a significant association between smoking history and smoking-related fear of health consequences (a). As such, in groups for whom the (protective) partially mediated channel (ab) is non-significant, the total effect (c) of life-time smoking exposure on thought given to screening is more negative. Figure 2 offers a visual representation of mediated effect differences across groups.

3.1. Robustness checks

We further explore two alternative path models with reversed arrows to compare to the proposed model. In the first reverse model for thought given to screening, smoking history is treated as the mediator variable and smoking-related fear of health consequences as the independent variable. In the second, smoking history is treated as the mediator and thought given to screening as the main predictor. Studies have suggested that the predicted mediation model is more convincing when reverse models identify non-significant indirect paths (34,35). We find that neither alternative model yields significant indirect effects, thereby conveying robustness of the predicted model.

4. Discussion

To the best of our knowledge, ours is the first study that systematically investigates the relationships between life-time smoking exposure, smoking-related fear of health consequences and thought given to lung cancer screening in a sample of high-risk prior and current smokers. Our results indicate that individuals at higher risk tend to contemplate lung cancer screening less. Moreover, we find that nearly a fourth of the adverse effect of smoking history on thought given to screening could be mediated through its effect on fear of smoking-related health consequences. Indeed, when the effect is mediated, smokers with higher risk profiles tend to contemplate screening more, suggesting that the mediator plays a significantly protective role. Considering the underlying mediational process revealed herein, interventions aimed at cultivating interest in screening among high risk current and prior smokers might benefit from invitation strategies and targeted education programs that communicate the health benefits of participating in screening whilst inspiring blame-free reflection.

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Table 1. Demographic, smoking history, quality of life and clinical characteristics across relevant groups, Italy 2018-19

		SRFHC					Thought given to LCS		
	Total (n=883)	Low (n=310)	Moderate (n=321)	High (n=252)	$\Delta_{1,2}$ P-value*	$\Delta_{1,3}$ P-value*	No (n=734)	Yes (n=149)	P-value*
Demographic									
Age	63.74 (6.77)	65.55 (6.61)	63.38 (7.09)	61.98 (5.99)	<0.0001	<0.0001	63.47 (6.74)	65.11 (6.77)	0.007
Gender, female[+]	326 (37%)	116 (29%)	146 (36%)	143 (35%)	0.001		269 (83%)	57 (17%)	0.711
Education[+]					0.101				0.006
Primary/lower secondary	569 (64%)	208 (37%)	195 (34%)	166 (29%)			456 (80%)	113 (20%)	
Upper/Post-secondary	293 (33%)	98 (33%)	119 (41%)	76 (26%)			259 (88%)	34 (12%)	
Tertiary	21 (2%)	4 (19%)	7 (33%)	10 (48%)			19 (90%)	2 (10%)	
Distance travelled (km)	152.50 (277.99)	110.02 (205.93)	168.74 (305.75)	183.70 (310.31)	0.009	0.002	151.86 (278.77)	155.66 (275.10)	0.888
Life-time smoking exposure									
Comprehensive smoking index	2.02 (0.37)	1.96 (0.45)	2.05 (0.33)	2.05 (0.31)	0.003	0.004	2.03 (0.37)	1.98 (0.37)	0.142
Quality of life									
SF-12 physical health score	21.16 (3.66)	21.81 (3.24)	21.34 (3.47)	20.11 (4.14)	0.078	<0.0001	21.21 (3.64)	20.91 (3.78)	0.363
SF-12 mental health score	22.71 (4.59)	24.02 (4.02)	22.90 (4.33)	20.89 (4.96)	0.002	<0.0001	22.74 (4.60)	22.58 (4.52)	0.716
Clinical									
Lung tumor, +diagnosis[+]	100 (11%)	40 (40%)	36 (36%)	24 (24%)	0.45		79 (79%)	21 (21%)	0.242
Other lung condition[++], +diagnosis[+]	292 (33%)	102 (35%)	103 (35%)	87 (30%)	0.825		233 (80%)	59 (20%)	0.063
Personal tumor history, yes[+]	95 (11%)	44 (46%)	28 (29%)	23 (24%)	0.052		78 (82%)	17 (18%)	0.779
Family tumor history, yes[+]	336 (38%)	112 (33%)	125 (37%)	99 (29%)	0.685		287 (85%)	49 (15%)	0.154
Body mass index	25.23 (4.01)	25.48 (3.71)	25.12 (4.33)	25.06 (3.94)	0.261	0.193	25.16(3.91)	25.54 (4.48)	0.295

SRFHC: Smoking-related fear of health consequences. [++]Other lung conditions include chronic obstructive pulmonary disease, emphysema and chronic bronchitis. Data are n(%) or mean(SD). Two-sided t-test to compare means between groups ($\Delta_{1,2}$ low vs. moderate SRFHC; $\Delta_{1,3}$ low vs. high SRFHC; thought given to screening vs. not). [+]x^2 test for independence of the difference between proportions for education, lung tumor/condition diagnoses, personal and family tumour history.

Table 2. Mediation of the effect of life-time smoking exposure on thought given to lung cancer screening (LCS), Italy 2018-19

		SRFHC						Thought given to LCS				
		β	SE	P-value	95% CI	R^2		β	SE	P-value	95% CI	R^2
Life-time smoking exposure (CSI)	a	0.17	0.07	0.021	0.03 to 0.31	0.10	c'	-0.32	0.12	0.006	-0.55 to -0.09	0.07
Smoking-related fear of health consequences (SRFHC)							b	0.34	0.06	<0.0001	0.23 to 0.45	
Age		-0.02	0.00	<0.0001	-0.03 to -0.02			0.02	0.01	0.001	0.01 to 0.04	
Gender, female		0.11	0.06	0.045	0.003 to 0.22			0.05	0.09	0.606	-0.13 to 0.23	
Education, ≥ upper secondary		0.08	0.05	0.112	-0.02 to 0.19			-0.36	0.08	<0.0001	-0.53 to -0.20	
Body mass index		-0.01	0.01	0.136	-0.02 to 0.003			0.01	0.01	0.430	-0.01 to 0.03	
SF-12 physical score		-0.04	0.01	<0.0001	-0.06 to -0.03			0.01	0.01	0.301	-0.01 to 0.04	
Personal tumor history		-0.15	0.08	0.072	-0.31 to 0.01			0.05	0.14	0.741	-0.23 to 0.32	
Family tumor history		0.00	0.05	0.995	-0.11 to 0.11			-0.01	0.09	0.886	-0.20 to 0.17	
Constant		4.17	0.40	<0.0001	3.39 to 4.95			0.92	0.71	0.200	-0.48 to 2.32	
Indirect effect	ab	0.06	0.03	0.034	0.004 to 0.11							
Indirect effect size		0.21										
Overall R^2		0.14										
Observations		883										

SE: Standard error; CI: Confidence intervals; CSI: Comprehensive Smoking Index. SEs and 95% CI generated from 1,000 bootstrap samples.

Table 3. Mediated effect of life-time smoking exposure (CSI) on thought given to lung cancer screening (LSC) through smoking-related fear of health consequences (SRFHC) by groups, Italy 2018-19

		Age <65					**Age ≥65**				
		SRFHC		Thought given to LCS			SRFHC		Thought given to LCS		
		β	95% CI		*β*	95% CI	*β*	95% CI		*β*	95% CI
CSI	*a*	0.003	-0.24 to 0.25	*c′*	-0.34*	-0.73 to 0.05	*a* 0.27***	0.11 to 0.43	*c′*	-0.35**	-0.64 to -0.06
SRFHC				*b*	0.39***	0.25 to 0.53			*b*	0.25***	0.07 to 0.44
Indirect effect	*ab*	0.001	-0.10 to 0.10				*ab* 0.07**	0.003 to 0.13			
Indirect effect size		0.004					0.23				
Overall R^2		0.10					0.13				
Observations		491					392				
		Women					**Men**				
		SRFHC		Thought given to LCS			SRFHC		Thought given to LCS		
		β	95% CI		*β*	95% CI	*β*	95% CI		*β*	95% CI
CSI	*a*	-0.06	-0.37 to 0.25	*c′*	-0.35*	-0.77 to 0.06	*a* 0.24***	0.09 to 0.39	*c′*	-0.34**	-0.62 to -0.05
SRFHC				*b*	0.40***	0.22 to 0.58			*b*	0.30***	0.17 to 0.44
Indirect effect	*ab*	-0.02	-0.15 to 0.10				*ab* 0.07**	0.01 to 0.13			
Indirect effect size		0.06					0.27				
Overall R^2		0.14					0.16				
Observations		326					557				
		Lower secondary					**Upper secondary and higher**				
		SRFHC		Thought given to LCS			SRFHC		Thought given to LCS		
		β	95% CI		*β*	95% CI	*β*	95% CI		*β*	95% CI
CSI	*a*	0.24***	0.07 to 0.40	*c′*	-0.27*	-0.57 to 0.03	*a* 0.02	-0.23 to 0.28	*c′*	-0.46**	-0.84 to -0.08
SRFHC				*b*	0.36***	0.21 to 0.50			*b*	0.29***	0.10 to 0.48
Indirect effect	*ab*	0.08**	0.01 to 0.16				*ab* 0.007	-0.07 to 0.09			
Indirect effect size		0.46					0.02				
Overall R^2		0.12					0.17				
Observations		569					314				
		≤Median SF-12					**>Median SF-12**				
		SRFHC		Thought given to LCS			SRFHC		Thought given to LCS		
		β	95% CI		*β*	95% CI	*β*	95% CI		*β*	95% CI
CSI	*a*	0.28***	0.08 to 0.49	*c′*	-0.25*	-0.54 to 0.04	*a* 0.08	-0.14 to 0.30	*c′*	-0.29*	-0.65 to 0.06
SRFHC				*b*	0.28***	0.14 to 0.41			*b*	0.33***	0.14 to 0.52
Indirect effect	*ab*	0.08**	0.005 to 0.15				*ab* 0.03	-0.04 to 0.10			
Indirect effect size		0.46					0.10				
Overall R^2		0.14					0.10				
Observations		397					384				

***p<0.01, **p<0.05, *p≤0.1. CSI: Comprehensive smoking index; SRFHC: Smoking-related fear of health consequences

Figure 1. Conceptual representation of the mediation model, Italy 2018-19

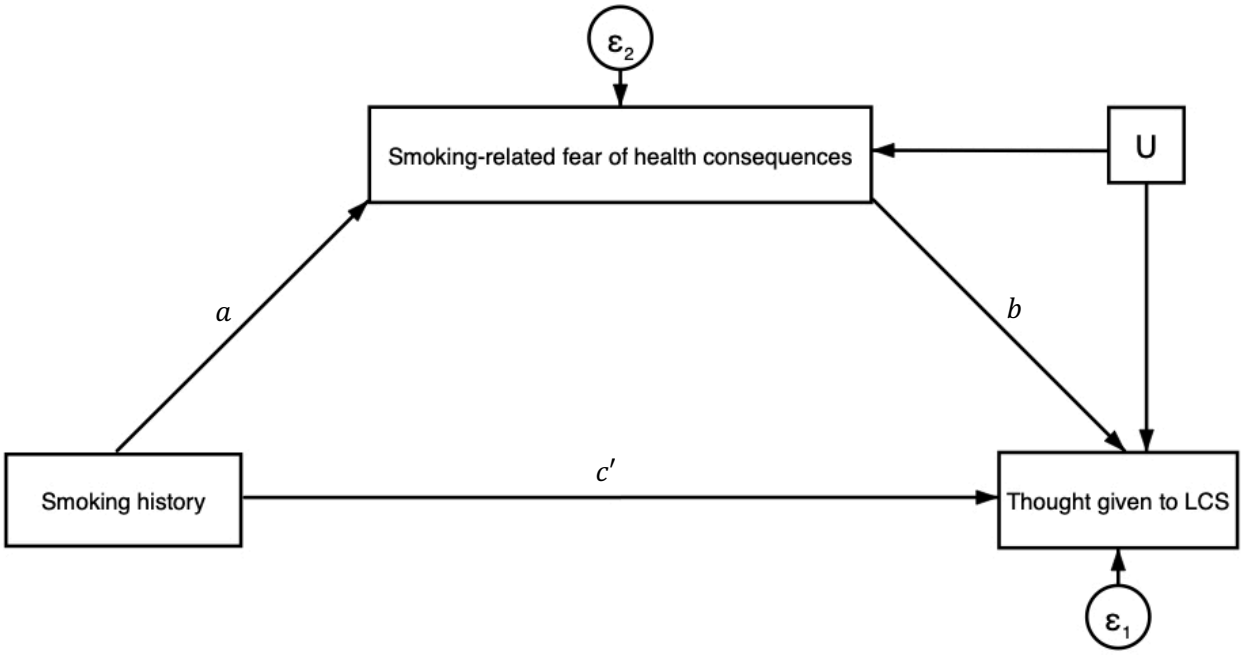
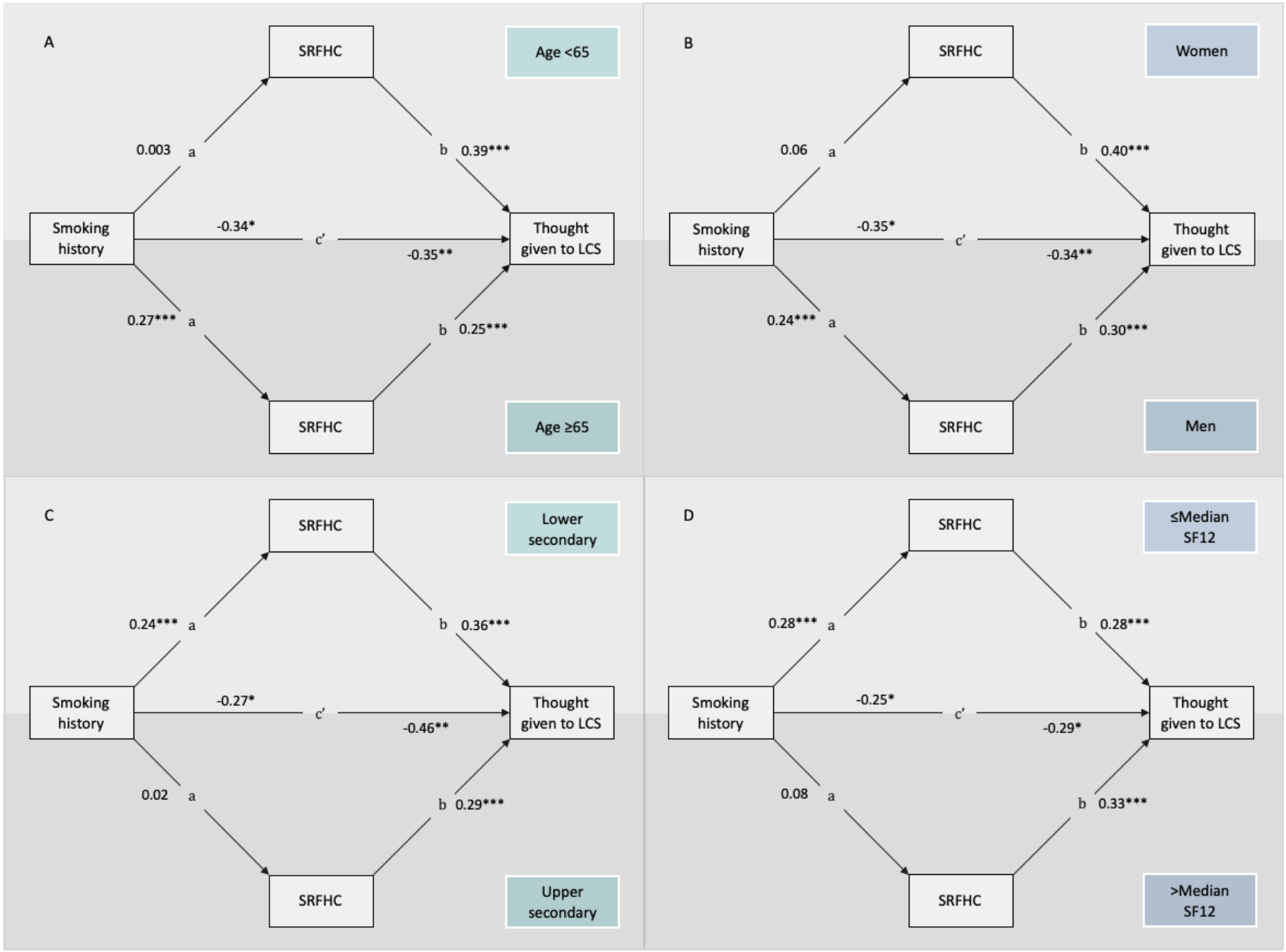


Figure 2. Mediated effect of life-time smoking exposure on thought given to lung cancer screening (LCS) by groups, Italy 2018-19.



***p<0.01, **p<0.05, *p≤0.1

Chapter 4

Cost-effectiveness and budget impact analyses of a population-based lung cancer screening program targeting high-risk prior and current heavy smokers in Italy

Abstract

Background
While the debate over the effectiveness of lung cancer screening programs is settled and its intrinsic policy appeal clear, issues regarding high false positive rates reported in screening trials warrant continued caution. Concerns around the mortality reduction benefits of lung cancer screening compared to its harms have been addressed through economic evaluation, however, available cost-effectiveness estimates differ substantially.

Methods
The objective of our modelling study is to assess the potential cost-effectiveness of a population-based lung cancer screening program targeting high-risk prior and current heavy smokers (≥20 pack-years) aged between 55 and 74 years, in Italy. The underlying model consists of a dynamic cohort-based Markov model with two components: (i) the natural history of disease progression and (ii) the treatment and aftercare paths corresponding to lung cancer stage at diagnosis. An important focus of our work is to estimate the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) of four specific LDCT-based screening invitation scenarios compared to standard clinical care. These include: (i) a standard invitation by local health authorities, (ii) a personalized invitation with endorsement from primary care physicians, (iii) a personalized invitation and a telephone reminder, and (iv) a personalized invitation, a telephone reminder and a transport offer. Costs and quality-adjusted life years (QALYs) are used as outcomes. Values for input parameters are estimated from the available literature, as well as from an ongoing lung cancer screening program in the Italian Lombardy region where possible. We conduct deterministic and probabilistic sensitivity analyses.

Results
Based on the assumption of an eligible high-risk population composed of 444,029 individuals in Italy, our cohort-based simulation resulted in an incremental gain ranging from 52,141 to 81,236 QALYs, and an incremental budget impact ranging from €771 million to €1.3 billion across the four screening scenarios over 15 years. Compared to standard clinical care, the ICERs for the analysed LDCT-based annual screening program scenarios vary between €14,527 and €16,040 per QALY gained. Thus, we offer evidence that rendering an annual LDCT-based screening – with three varying screening invitation strategies – available to the Italian heavy smoker population is more effective, yet more costly, than current clinical practice from the perspective of the national budget holder.

Discussion
Overall, our modelling study for the Italian context reveals that population-based LDCT lung cancer screening is cost-effective for a number of different screening invitation scenarios. Our findings offer robust support for policy makers, payers and guideline developers who are faced with the important decision of whether to implement population-based, life-saving, lung cancer screening programs. Moreover, we provide evidence that the comparative effectiveness of different invitation strategies intended to improve engagement with the high-risk population of ever smokers generates sufficient variation in uptake so as to increase the cost-effectiveness of strategies.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality and the most common type of cancer worldwide (1). Its incidence is most pronounced among older current and prior heavy smokers (2), and while early detection is the strongest predictor of survival (3), most cases present at advanced stages (4). In recent years, the debate over the value of lung cancer screening has intensified with the conclusion of several large-scale randomized trials in Europe and the U.S. Indeed, the U.S. National Lung Screening Trial (NLST) offers convincing evidence that annual low-dose computed tomography (LDCT) screening effectively reduces the relative risk of lung cancer mortality by 20% (5). Echoing these findings, thoracic LDCT screening for active or prior heavy smokers at high risk of lung cancer is now an evidence-based, Medicare-covered test (6) recommended by the U.S. Preventive Services Task Force (7). In parallel, European mortality data has recently become available from the NELSON randomized controlled trial, revealing LDCT screening to be associated with lung cancer mortality reductions of 26% in men and 39-61% in women (8). Findings from the U.K. Lung Cancer Screening Trial (UKLS) reveal that 75% of cancers diagnosed through LDCT were stage 1, thus expected to have optimistic 5-year survival. Aligned with trial-based conclusions, evidence from the International Early Lung Cancer Action Project (I-ELCAP) – a meta-analysis of several international observational studies – confirms that the mortality reductions attributable to lung cancer screening are due to a significant stage shift effect (9). In this respect, accruing clinical evidence suggests that well-targeted lung cancer screening programs may lead to substantial health benefits among high-risk patients, giving their known potential to reduce mortality through early detection.

While the debate over the effectiveness of lung cancer screening programs is settled and its intrinsic policy appeal clear, issues regarding high false positive rates reported in screening trials warrant continued caution. Indeed, extensive discussion has ensued as to whether the potential harms incurred in achieving a diagnosis among asymptomatic individuals – including the risk from radiation and the notable psychological impact of investigation and treatment – outweigh the relative merits of early detection (10). Though concerns around the mortality reduction benefits of lung cancer screening compared to its harms have been addressed through economic evaluation, available cost-effectiveness estimates differ substantially. Early studies from Canada and the U.S. find that the cost-effectiveness of screening programs ranges between C$52,000 and US$81,000 per quality-adjusted life year (QALY) (11,12), while studies reflecting the European context reveal estimates varying from €1,353 and €30,291 to €69,099 per QALY in Poland, Germany and Switzerland, respectively (13–15). Unsurprisingly, the observed heterogeneity of cost-effectiveness estimates is greatly influenced by non-negligible cross-country differences in lung cancer incidence, screening costs and participation rate. Yet, while the highest sensitivity is consistently observed for the rate of newly developed cancers, Hofer et al. show that varying the adherence rate of the eligible population from 27% to 81% generates incremental cost-effectiveness ratios (ICERs) corresponding to €24,600 and €17,500 per QALY, respectively (14). This highlights the economic relevance of programs designed with a view towards improving screening participation within hard-to-reach target populations.

Resulting from the population's behavioural response to the programmatic characteristics of screening invitation strategies (16–18), participation rate inherently signals the attractiveness of screening initiatives. And, although encouraging preventative care-seeking behaviour among prior and current heavy smokers is an undeniably tall order considering the population's tendency to forgo screening (19–21), it is one among few modifiable aspects that may optimize the cost-effectiveness of well-targeted programs. The literature is replete with evidence showing the comparative effectiveness of invitation strategy types on cancer screening adherence rates (22). However, whether different invitation strategies could generate sufficient variation in participation so as to make some programs significantly more or less cost-effective than others, is not clear. The objective of the present modelling study is to assess the potential cost-effectiveness of a population-based lung cancer screening program targeting high-risk prior and current heavy smokers in Italy from a payer perspective. Moreover, we aim to estimate the ICER of each of four specific invitation scenarios compared to no screening.

2. Methods

The model assesses the costs and effectiveness of an annual LDCT-based lung cancer screening program targeting high-risk current and prior heavy smokers in Italy and compares these to those expected in the absence of an organized screening program. The model can be characterized by its component parts: first, we simulate the period of disease progression before diagnosis (*i.e.* the natural history component), and second, we simulated the clinical pathways associated with a diagnosis (*i.e.* treatment and aftercare component). In so doing, our aim is to capture the benefits of early detection that may be attributed to a national lung cancer screening program in Italy. Though the model runs two main scenarios: one with an annual LDCT-based lung cancer screening and another where diagnosis occurs via usual clinical care (*i.e.* when patients present and are diagnosed after the onset of clinical symptoms), a further objective of our modelling study is to assess the potential cost-effectiveness of different screening invitation strategies. Hence, we compare the usual care scenario with four invitation strategies with increasing implementation costs and screening adherence rates. Outcomes of this cost-effectiveness analysis (CEA) are costs and QALYs gained, while our main outputs are the ICER and the Net Monetary Benefit (NMB) for annual screening program scenarios compared to usual care.

We define the target high-risk population eligible to attend the screening program as prior or current heavy smokers (≥20 cigarettes per day) aged between 55 and 74 years, which closely resembles the recommended risk profile of the U.S. Preventive Service Task Force (7). Based on data from the Italian National Institute of Statistics corresponding to heavy smoking habits across 5-year age groups in 2019 (23), we estimate a cohort size of 444,029 high-risk individuals. We use a cycle length of 3 months and run the model for 60 cycles (*i.e.* 15 years). We applied within-cycle correction to mitigate the over-estimation problem of traditional Markov models, whereby we estimate cycle rewards based on the cohort percentage in each state at both the start and the end of the cycle (24). Costs and QALYs are discounted by 3% per year. The model is built and calibrated in TreeAgePro and Excel.

2.1. Model structure

Ours is a cohort-based Markov model consisting of two components that distinguish between (i) the natural history of disease progression and (ii) treatment paths and aftercare depending on patients' lung cancer stage at diagnosis. The natural progression component of our model consists of 9 states, representing lung cancer stages IA to IV, a state of no apparent lung cancer and two states for death (*i.e.* due to lung cancer and due to other causes). Figures 1 and 2 depict the possible transitions in a model with and without LDCT screening, respectively. In each scenario and within each cycle, individuals who develop lung cancer may: (i) progress to a higher stage, (ii) remain in their current stage, (iii) get diagnosed, or (iv) die from lung cancer and other causes. The input matrix corresponding to the natural history of lung cancer – containing transition probabilities between lung cancer states and incidence rates – was calibrated to known incident and prevalent cancer detection rates in Italy (25) using Powell's bound optimization by quadratic approximation (BOBYQA) method (26). The BOBYQA algorithm employs stochastic behaviour to determine optimal input values through an iterative process – thus, resulting in an evolving set of input parameter sets seeking to move towards a better fit of target empirical data with each iteration. We used the recommended weighted sum of square differences to assess the goodness of fit between model-predicted endpoints and target epidemiological estimates, including stage-specific cancer prevalence rates (27,28). Tables 1 and 2 present transition probabilities for the natural history module across usual care and LDCT screening scenarios, respectively.

The simulated cohort enters the second component of our model after diagnosis, in which treatment and aftercare are assigned corresponding to each stage of lung cancer. This module includes 5 states for treatment, 4 states for aftercare and a state for death. Figure 3 presents the possible transitions of the post-diagnosis module. Treatment paths are designed according to Italian clinical practice guidelines, while treatment allocation is based on the Italian ITALUNG trial (25) (Table 3). The probability of entering the post-diagnosis component of the model differs between high-risk individuals who attend the annual LDCT screening and those who are diagnosed through standard clinical care after the onset of symptoms. We estimate transition probabilities between treatment and aftercare states using the available literature (29,30) (Table 4). We assume that annual screening follows the same protocol of the Smokers' Health Multiple Actions program (SMAC), the first free LDCT lung cancer screening program in Italy implemented at the Humanitas Research Hospital, which focuses on nodule (∅) type and size, as well as volume-doubling time (VDT). Figure 4 presents the screening algorithm.

We build two model types. The first considers a homogenous cohort of size 1, as most traditional cohort-based Markov models do when reporting costs and effectiveness as average values for a typical individual. The second considers a cohort of 444,029 high-risk individuals, whose size changes over time (Table 5). Prior to the start of the first cycle, we define the distribution of the simulated high-risk cohort across relevant states of the natural disease progression module (*i.e.* No lung cancer and Stages I-IV). The distribution across states is based on Pegna et al.'s (25) prevalent cancer detection rate findings from the first

screening round of the ITALUNG randomized control trial, which evaluates the efficiency of LDCT-based lung cancer screening in the Tuscany region of Italy. Moreover, the dynamic Markov model adds 26,699 high-risk individuals to the cohort each year, who represent the population of 55 year-old current and former heavy smokers in Italy (23). Likewise, we estimate the distribution of cohort entries across natural disease progression states from the ITALUNG trial (25).

By building a corresponding Markov model with a dynamic cohort size we are able to assess how the introduction of LDCT screening for the population of high-risk prior and current heavy smokers in Italy impacts the budgetary trajectory of the Italian National Health Service, from the perspective of the budget holder. While the traditional Markov model allows us to estimate the additional benefit of lung cancer screening in relation to its cost for a typical patient, with the dynamic cohort model, we further estimate the expected budgetary impact of LDCT-based screening alternatives in Italy over a 15-year implementation time horizon.

2.2. Model parameters

a. Effectiveness of screening and invitation strategies

The sensitivity per lung cancer screening stage with LDCT is estimated from ten Haaf et al.'s findings from the NLST and Prostate, Lung, Colorectal, and Ovarian (PLCO) trials (31). We assume that lung cancer screening adherence is equal to that for established colorectal cancer screening programs in Europe (32). Table 6 presents all estimations for relevant screening parameters.

As it regards invitation strategies, we consider: (i) a usual invitation by local health authorities, (ii) a personalized invitation with endorsement from the individual's primary care physician, (iii) a personalized invitation and a telephone call within five days of the screening appointment to confirm receipt of invitation letter and remind invitee of upcoming appointment, and (iv) a personalized invitation and an offer of private transport reimbursement to the screening centre. We estimate the comparative effect of these invitation strategies on screening adherence rate from various sources. First, Wardle et al. (32) conduct a cluster-randomized controlled trial (n=264,325) to evaluate the effect of a personalized invitation letter with the endorsement of the general practitioner (GP), compared to a standard invitation letter, on colorectal cancer screening uptake among individuals aged 60-74 years in the UK. Their findings show a slight but significant percentage point differential (0.7 p.p.) in uptake between standard invitation and invitation with GP endorsement (57.5% vs. 58.2%), with the adjusted odds ratio in favour of the intervention 1.07 ($p>0.0001$).

Second, Offman et al. (17) conduct an observational study of a planned screening invitation strategy (n=10,928) to assess the effect of a telephone reminder intervention, compared to a GP-endorsed invitation letter, on breast cancer screening uptake among women aged 50 to 70 years in the UK. Those invited for breast screening were called within five days of the screening appointments, aiming to (1) confirm receipt of the invitation letter, (2) remind

invitees of their upcoming appointment, (3) answer basic questions, and (4) correct misapprehensions by providing information on the expected benefits and risks of screening. They show a significant ten percentage-point increase in screening attendance rates between individual practices that implement the telephone reminder intervention, compared to practices that do not (67% vs. 57%), in favour of the former.

Finally, though to the best of our knowledge, there are no studies assessing the effect of interventions offering transport to the screening appointment on adherence, Wang et al. (33) conduct a district-level spatial analysis (n=162,573) assessing the effect of car ownership on breast cancer screening attendance among women aged 50 to 70 in the UK. Their results indicate that when the average household car ownership increases by one, the odds of taking up breast cancer screening increase by a factor of 1.51, holding all other demographic and socio-economic variables constant. We assume that the absence of car ownership can be mitigated by an offer of private transport to the screening appointment – all the while acknowledging that our assumption is strong yet indispensable in the context of the literature's lacunae.

We calculate percentage-point increases based on Wang et al.'s findings. Assuming that the base rate for success is 68.2% (*i.e.* success in the control group that receives a GP-endorsed invitation and a reminder telephone call) and that OR=1.51 (*i.e.* effect of car ownership on breast cancer screening attendance), then the success rate in the intervention group (*i.e.* group receiving a GP-endorsed invitation, a reminder telephone call, *and* an offer of private transportation) is:

$$P_{intervention} = \frac{OR * P_{control}}{1 + (OR * P_{control}) - P_{control}} \quad (1)$$

This results in an 8.2 percentage-point increase in favour of the intervention offering a GP-endorsed invitation, a reminder telephone call *and* an offer of private transportation compared to the group that does not receive the transportation offer (76.4% *vs.* 68.2%). Hence, the accrued literature investigating the comparative effect of invitation strategies on adherence (17,32,33) allows us to derive incremental adherence rates corresponding to screening invitation strategies that offer increasing levels of engagement and ease to the targeted population (Table 6).

b. Mortality

Our model assumes that all-cause mortality does not differ between those who are diagnosed through standard clinical care and those who are diagnosed pre-clinically via LDCT-based screening. For individuals without apparent lung cancer, we derive death rates from mortality tables corresponding to the Italian general population (34,35). Mortality assigned to each lung cancer stage of the natural disease progression module is informed by findings from a systematic review (36) and calibrated using the BOBYQA method (26). Moreover, we project mortality rates for each treatment and aftercare state of the post-diagnosis model component using estimates from a known systematic review (29). Finally, our model

considers: (i) time-varying mortality rates across the 15-year time horizon intending to reflect upon the age-specific probability of dying of an ageing cohort, which (ii) we adjust by means of a time-dependent hazard ratio relevant to a high-risk prior and current heavy smoker population (37).

c. Quality of life

For individuals without a lung cancer diagnosis transitioning through the natural disease progression module – as well as for those with undetected early lung cancer (*i.e.* Stages I and II) – we assign a baseline quality of life score (38). In addition, we assume that current and former heavy smokers with advanced, albeit undetected, lung cancer (*i.e.* Stages IIIA/B and IV) have relatively lower quality of life compared to their counterparts with early disease. Indeed, the literature extensively reports that high-risk individuals with a life-time history of smoking tend towards fatalism, thereby neglecting to acknowledge the onset of symptoms (*e.g.* productive cough, haemoptysis, fatigue) and postponing clinical consultation for fear of diagnosis (39–41). Table 7 presents the utility associated with undetected, advanced lung cancer stages, which we assume to be both lower than that of early stages and higher than that associated with the respective stage-specific treatment. As it regards the post-diagnosis model component, we use pooled quality of life scores available from a meta-analysis (42) corresponding to each lung cancer treatment and aftercare state. Furthermore, we consider the expected impairment of quality of life for individuals undergoing unnecessary positron emission tomography (PET)-guided biopsies following similar approaches in the literature (14,43). These are individuals whom the LDCT misdiagnoses as suspect cases but are not subsequently diagnosed with lung cancer when screened with more invasive procedures (*i.e.* false positives).

d. Costs of diagnostic procedures

The cost of diagnosis in the cohort that actively consults a physician after developing clinical symptoms is comprised of the following components: (i) a medical history consultation with a general practitioner, (ii) a chest x-ray, (iii) an ultra-sound scan, (iv) a contrast-enhanced CT scan, (v) an MRI scan for staging, and (vi) a bronchoscopy. We derive prices associated with these procedures from Italian national-level reimbursement tariffs (44,45). In parallel, the cost of the screening program is comprised of (i) a 30-minute encounter with a registered nurse, (ii) a 30-minute encounter with a radiology technician, (iii) a consultation with a radiologist, and (iv) a non-enhanced LDCT scan. Moreover, following the LDCT screening, individuals with suspect nodes requiring further examination undergo (v) a PET-guided biopsy and (vi) a consultation with a pulmonologist. The costs of consultation with medical professionals are derived from Italian national decrees and collective contracts establishing minimum salaries for medical professionals in public institutions (45–48).

e. *Costs of screening invitation strategies*

The cost components comprising the first invitation strategy (IS1: Usual invitation) include: (i) an administrative lump sum representing invitation costs commonly incurred in structured

screening programs (14) and (ii) an invitation letter postage (49). The cost items comprised in the second invitation strategy (IS2: GP-endorsed invitation) include: (i) a higher administrative lump sum and (ii) invitation letter postage (49). In effect, we assume based on Wardle et al. (32) that the administrative costs incurred by a program that contacts GPs and obtains lists of individuals fitting the target population characteristics from GP practices would be at least 1.5 times that of a program that contacts the target population directly via usual invitation.

The cost items comprised in the third strategy (IS3: GP-endorsed invitation and telephone reminder) are the same as those of IS2, with the addition of (i) training for clerical staff dedicated to conducting calls and (ii) a 10-minute engagement with a trained caller. As described in Offman et al. (17), callers should attend one training programme covering a general overview on lung cancer screening, including its expected benefits and risks, informed consent and information governance. Considering the sensitive topical content, we assume that a comprehensive caller training should consist of 16 hours. Moreover, assuming that each caller contacts 48 individuals belonging to the high-risk cohort in an 8-hour working day. It would require 150 callers – each making 48 calls per day, and collectively making 7,200 calls per day – to reach the target population of 444,029 former and current heavy smokers in 61.7 working days. Thus, we estimate that the minimum number of callers needed to reach the target population in a reasonable time frame to be 150. It follows that a 16-hour training programme for 150 minimum wage clerical staff yields an overall training cost of €22,440, which we divide by the target population size.

Finally, the fourth invitation strategy (IS4: GP-endorsed invitation, telephone reminder and transportation offer) includes the same cost items as IS2 with the addition of (i) a lump sum representing the offer of private transport to the screening centre (50). Using data from high-risk individuals who attended the first free LDCT lung cancer screening program in Italy between 2018 and 2019 at the Humanitas Research Hospital (n=1,112), we estimate that the median distance travelled by individuals attending screening is 50 kilometres. Moreover, assuming that the offer of private transport is extended to every individual in the high-risk cohort, we should expect that at least 20% of them to accept giving that 80% of Italian households own at least one car. As such, offering private transport to the target population of current and former heavy smokers should result in 91,606 (€100 flat-rate) round trips to screening centres, which we divide by the target population size to obtain a lump sum per invitee.

f. Costs of treatment and aftercare

We estimate inpatient costs for each of the five typical treatment regimens that tend to follow a lung cancer diagnosis according to the literature (51). The cost of aftercare was agreed upon in consultation with physicians at Humanitas Research Hospital and San Raffaele Hospital in Italy, and are aligned with those presented in previous studies (14). The costs of treatment and aftercare apply equally to lung cancer patients diagnosed through annual LDCT screening as well as those diagnosed through standard clinical care. Table 8 details the costs associated with screening, diagnostic, treatment, and aftercare procedures.

2.3. Sensitivity analysis

We conduct deterministic one-way sensitivity analyses to explore the sensitivity of our model to relevant parameters, including: (i) costs associated with the LDCT-based screening program, (ii) costs associated with screening invitation strategies, (iii) LDCT test sensitivity in early lung cancer stages, (iv) probability of progressing from no lung cancer to stage I, (v) overall and annual entry cohort sizes, (vi) number of cycles and (vii) annual discount rate. In addition, we perform probabilistic sensitivity analyses with 10,000 Monte Carlo Markov Chain (MCMC) simulations to account for generalized parameter uncertainty, by drawing randomly from normal, beta, gamma and Dirichlet distributions (Tables 1-8).

3. Results

Our model predicts a surplus ranging from 0.08 to 0.13 QALYs gained per person across the screening scenarios analysed, compared to usual care. Table 9 presents the base-case cost-effectiveness analysis findings for both dynamic and traditional Markov cohorts. ICERs and NMBs are presented incrementally based on ranked LDCT-based screening scenarios, as well as relative to the usual care baseline comparator. Figure 5 further illustrates the incremental cost-effectiveness across simulated scenarios. Excluding the extendedly dominated LDCT screening with GP-endorsed invitation (IS2), all screening scenarios analysed are undominated and reasonably cost-effective for a payer willing to spend up to ~€20,000 per QALY gained.

The average cost per person amounts to €3,252 in the usual care cohort and from €4,471 to €5,349 in the four alternative screening scenarios. Based on the assumption of an eligible high-risk population composed of 444,029 individuals in Italy, our cohort-based simulation resulted in an incremental gain ranging from 52,141 to 81,236 QALYs, and an incremental budget impact ranging from €771 million to €1.3 billion across the four screening scenarios over 15 years. Compared to standard clinical care, the ICERs for the analysed LDCT-based annual screening program scenarios vary between €14,527 and €16,040 per QALY gained. Thus, we offer evidence that rendering an annual LDCT-based screening – with three varying screening invitation strategies – available to the Italian heavy smoker population is more effective, yet more costly, than current clinical practice from the perspective of the national budget holder.

Table 10 presents resource consumption across usual care and screening scenarios over 15 years of program implementation. We reveal that cost differences between usual care and screening scenarios are mainly attributable to the high frequency of LDCT procedures (from 5.97 to 9.4 million) and PET-guided biopsies (from 39,566 to 61,372) performed in the screening cohorts over 15 years. Moreover, we observe a substantial stage shift effect in lung cancer diagnosis induced by the LDCT screening program. Frequency of resource consumption across screening cohorts is substantially higher among the first two lines of lung cancer treatment (*i.e.* 'Surgery' and 'Surgery + Chemotherapy'), thereby indicating that a greater number of diagnoses occur at preclinical stages (I-II).

Nevertheless, across screening invitation strategy scenarios, there is a non-negligible proportion of the high-risk cohort that does not adhere to the LDCT screening program (from 23.6% in IS4 to 42.5% in IS1) – and hence progresses to advanced stages prior to diagnosis via clinical presentation. As such, we observe that resource consumption within the third and fourth lines of lung cancer treatment (*i.e.* 'Surgery + Chemotherapy + Radiotherapy' and 'Chemotherapy + Radiotherapy') is maintained across usual care and screening cohorts. Likewise, due to the vast segment of non-adherers in the eligible population, consumption of palliative care resources is maintained across usual care and screening cohorts. Finally, since lung cancer survival improves with LDCT screening, we find an increase in aftercare resource consumption related to periodic follow-up visits sustained for a longer period of time. Overall, across LDCT invitation scenarios, we find that the new therapeutic mix is characterized by a higher composition of early lung cancer therapies relative to the usual care mix, which is skewed towards advanced-stage care. Treatments for early disease stages fail to replace those targeting advanced stages, as the latter are relevant, nonetheless, for an important segment of the high-risk cohort that foregoes participation in the screening program across invitation strategies.

Figure 6 illustrates ICER tornado plots comparing ranked undominated strategies: (i) LDCT screening with IS1 (standard letter) vs. usual care, (ii) LDCT screening with IS3 (GP-endorsed letter + telephone reminder) vs. IS1, and (iii) LDCT screening with IS4 (GP-endorsed letter + telephone reminder + transport offer) vs. IS3. We observe the highest sensitivity for the cost associated with the LDCT-based screening program, as well as that associated with invitation strategy types. The LDCT scan sensitivity in the presence of early stage lung cancer and the rate of newly developed cancers also have a comparatively large influence on the ICERs. In contrast, cohort size, cohort entry size, number of cycles and annual discount rate alter the ICERs to a limited extent.

Table 11 presents detailed deterministic sensitivity analysis results for the dynamic Markov cohort model across undominated strategies, conveying robustness of the estimated ICERs and NMBs across ranked LDCT-based screening scenarios. Overall, the model results are convincing, with no parameter variation exceeding ~€32,000 per QALY gained. The Monte Carlo simulation revealed average ICERs for the analysed LDCT-based annual screening program scenarios (IS1 through 4) ranging from €15,923 to €17,590 per QALY gained, compared to standard clinical care. These are slightly above our base case ICERs. We show the incremental cost-effectiveness scatter plots corresponding to 10,000 simulation draws, which compare undominated invitation strategies to the usual care scenario (Figure 7), as well as according to ranking (Figure 8). Figure 9 reveals that an LDCT screening program with a high engagement invitation strategy (IS4: GP-endorsed letter + telephone reminder + transport offer) is consistently the strategy with the highest cost-effectiveness likelihood once the budget holder's willingness-to-pay exceeds ~€34,000 per QALY gained.

4. Discussion

We offer evidence of the cost-effectiveness of a population-based lung cancer screening program in Italy targeting high-risk prior and current heavy smokers aged between 55 and 74 years, from the perspective of the national health budget holder. To our knowledge, we are the first to integrate the comparative effectiveness of invitation strategies on adherence to screening in the economic evaluation of screening intervention scenarios. In so doing, we assess the cost-effectiveness of a lung cancer screening program designed with increasing levels of engagement vis-à-vis the eligible population and, thus, a view towards improving screening participation. Our findings reveal that rendering an annual LDCT-based lung cancer screening – with three varying levels of engagement across invitation strategies – available to the Italian heavy smoker population is more effective, yet more costly, than current clinical practice. Although there is no official cost-effectiveness threshold in Italy for accepting or rejecting health interventions, compared to the usual care scenario, the population-based lung cancer screening program (IS1) would be regarded as cost-effective (ICER: €14,794), according to both the country-specific, PPP-adjusted threshold proposed by Woods (~€17,928) (52), and that proposed by the WHO (~€28,773) (53). Notably, three of the four screening invitation strategies analysed lie at the cost-effectiveness efficiency frontier. Moreover, even when coupled with increasingly costlier invitation strategies (IS3 and 4), lung cancer screening remains an acceptable cost-effective alternative to usual care (ICERs: €15,531–€16,326) considering the afore indicated willingness-to-pay thresholds.

Several previous cost-effectiveness studies of lung cancer screening programs in Europe have yielded similar results for high-risk populations. A German microsimulation study reported ICERs of efficient screening scenarios, with varying selection criteria and thresholds for nodule size and growth rate, ranging between €16,754 and €23,847 per life year gained (54). However, the vast majority of studies reflecting the European context reveal estimates varying from £8,466 and £10,069 (55,56) to €30,291 and €69,099 (14,15) per QALY gained. Aside from different modelling approaches, the observed heterogeneity of cost-effectiveness estimates is attributed to distinct assumptions informed by non-negligible cross-country differences in lung cancer incidence, screening costs and participation rates. Recently, a study based on a decision tree analysis reflecting the Italian context found lung cancer screening to be cost-effective (ICER: €3,297 per QALY) (57). Though our findings share the favourable resolve that implementing a population-based lung cancer screening in Italy would be cost-effective – as well as an analogous incremental effect of screening (.08 QALY) – our ICER estimates are considerably higher. Indeed, on first glance, our models make several diverging assumptions that may have reasonably widened the distance between our estimates – not least of all the fact that there is a 10-year difference between the time horizons that we consider.

First, while we assume that LDCT sensitivity is dependent upon lung cancer stage and therefore varies between 43.4% (stage I) and 97.8% (stage IV), Veronesi et al. apply a fixed 90% LDCT sensitivity across stages. Second, while our model considers screening interventions with adherence ranging between 57.5% (IS1) and 76.4% (IS4), theirs assumes a considerably higher compliance of 79%. Third, costs associated with LDCT screening sessions are remarkably distinctive between our models – while we derive the cost of a single

LDCT session from the procedure's reimbursement as well as the time allocated by health professionals to perform the procedure (€102), Veronesi et al. assess a significantly lower estimate per session (€63), which does not account for the human resource component. Finally, our estimates of the administrative costs associated with screening are, substantially different – whilst ours range between €32 and €69 depending on invitation strategy, theirs are fixed at €17. Indeed, Veronesi et al. acknowledge that the incremental cost of screening estimated by their model constitute this literature's lower bound. Thus, we argue that the divergence between our modelling approaches and parameter assumptions explain why we may consider Veronesi et al.'s findings to be reasonable lower bound estimates of the cost-effectiveness of lung cancer screening in Italy, while ours comprise a range of upper bound estimates corresponding to a screening intervention with varying invitation strategies.

Considering the voluntary nature of participation and the challenges of engaging an ever-smoker population (39,40) – that often disregards prevention due to the stigma surrounding lung cancer and the fatalistic beliefs associated with a diagnosis – we opted towards conservative levels of adherence. The literature evaluating the cost-effectiveness of population-based lung cancer screening in European countries reveals ample heterogeneity when reflecting upon compliance. While some assume near perfect (85-100%) and cautiously optimistic (79%) levels of participation (15,54,57), others gage decisively lower estimates (45-54%) (14,58). We elected to fall within the conservative end of the spectrum when modelling our cohort's adherence to screening, guided, in part, by findings from a recent European trial and pilot program revealing that 15-31% of eligible contacted persons respond positively and are willing to engage with 'lung health checks' leading to screening (55,56). Indeed, the high-risk population that lung cancer screening programs hope to engage differs from those targeted for other types of screening in one important respect – smokers, who battle a nicotine addiction, often experience blame related to the perceived self-infliction of tobacco-related diseases secondary to life-style choices (41). Thus, it is reasonable to assume that this population may be difficult to reach, and their interest harder to maintain in a recurrent, long-term prevention program.

Furthermore, we underline a crucial difference in the manner through which we treat adherence, which, we argue, sets us apart from modelling studies published thus far. Others have shown that ICERs tend to be highly sensitive to changes in adherence rates. However, introducing variations in adherence in the later stages of the modelling exercise neglects the fact that improvements can and should be an integral part of the design of mass prevention programs. Our model embeds adherence in the design of the screening intervention, as such, improvements in terms of the eligible population's intended participation across screening scenarios result from improvements in the design of interventions. The crux of the matter is that designing interventions that understand and rise to the challenge of compliance in a hard-to-reach population implies further, non-negligible costs. We consider, for instance, that the administrative effort necessary to bring about the invitation strategy with the highest level of engagement and ease of participation (IS4) – thus resulting in the highest adherence (76%) – incurs a cost (€69) comparable to that of the LDCT screening session (€102). Indeed, though it is tempting to dismiss the task of a caller reminding a person of her upcoming appointment, offering information about the procedure, and arranging transport to her appointment *vis-à-*

vis that of a technician examining a scan of her lungs, both are necessary, and neither is sufficient to the success of a population-based mass screening program.

Undervaluing the non-medical human resources needed to run such a program leads to a correspondingly gross underestimation of the costs incurred to build its capacity, as well as to a missed opportunity. When leveraged to serve a unique population that battles a life-time addiction, the stigma of a self-inflicting behaviour, the fatalism of a diagnosis and the fear of knowing, trained non-medical resources may make it easier, more acceptable, and less frightening for current and former heavy smokers to participate in annual lung cancer screening. And, though it is an indisputably tall order, a wealth of literature has accrued with the sole purpose of examining the comparative effectiveness of invitation strategies on cancer screening uptake, with encouraging findings (16–18,32,33,59). Incorporating these into our understanding of screening adherence, and the programmatic avenues that can be explored to improve it, enriches our models – narrowing the gap between what we know and how we model it. When we compare the three undominated lung cancer screening interventions with varying invitation strategies (IS1, IS3 and IS4) across a continuum of adherence, we find that each has a unique cost-effectiveness trajectory compared to the usual care scenario (Figure 10). In this regard, while our informed base-case estimates of adherence for each invitation strategy evaluated lie at the higher end of the scale, a payer bound to judge cost-effectiveness under a fixed WTP threshold should consider the effect that lower levels of adherence to screening may have on the interventions' ICERs.

Our findings reveal that LDCT-based lung cancer screening, with varying invitation strategies, results in an incremental life-year gain ranging between 63,719 (IS1) and 98,939 (IS4) over 15 years, when compared to the usual care scenario. As such, screening offers notable improvements in the eligible population's quality, and length of life. This raises a fundamental, albeit contentious, issue within our cost-effectiveness analysis, centred on the future unrelated medical costs consequent of the life-extending nature of a screening intervention targeting an ageing population (60–62). Indeed, when considering a fixed health care budget, interventions like ours, which succeed in prolonging life, must acknowledge non-negligible health opportunity costs that result from lowering the budget per person for health care in the future. Whilst previous cost-effectiveness studies of lung cancer screening in Europe have implicitly excluded future unrelated medical costs from their analyses, we believe ample theoretical work (60,63), empirical applications (64–66), and practical guidance exist (67) to support their inclusion in ours. Thus, we submit that accounting for the unrelated medical costs expected to arise in the future life-years of a high-risk ever-smoker population – which would not have been lived in the absence of screening – is aligned with the decision maker's objective of maximizing health benefits in the context of a fixed budget.

We use a known practical application to include future disease costs (PAID 3.0) in estimating the unrelated medical costs associated with the life-extending effect of a population-based screening intervention targeting lung cancer (67,68). In so doing, we linked age-, sex-, and disease-specific per capita medical spending with projected survival curves derived from our cohort-based Markov model for each intervention arm (*i.e.* usual care *vs.* LDCT-LCS scenarios). Though the tool estimates disease-specific per capita healthcare spending using

Dutch cost of illness data, we consider reasonable to assume health care use for unrelated diseases in Italy to resemble that of the average population in The Netherlands (69). Figure 11 reveals a pattern of rising unrelated healthcare expenditure with age, thereby anticipating that the impact of their inclusion on the ICER of screening *vis-à-vis* usual care may increase with higher ages. Per capita annual health care expenditure for diseases unrelated to lung cancer – yet, associated with living one additional year due to the presence of screening – also increases with age. We estimated that the impact of including future unrelated medical costs on the ICER when the lives of the eligible ever-smoker population are prolonged by lung cancer screening corresponds to an additional €1,738 per QALY gained. Thus, whilst the inclusion of future costs increases our ICER estimates, the cost-effectiveness of lung cancer screening compared to usual care (IS1: €16,532 – IS4: €18,064) is maintained below a €20,000 WTP ceiling.

An important practical issue to consider when seeking to implement a population-based lung cancer screening program in Italy regards the spatial availability of equipment and specialized human resources for health across the territory. Research has shown that uptake of mass cancer screening tends to be associated with physician density (70–72), and importantly, with distance and travel time to health facilities (18,73). In this regard, it is relevant to question how quickly and equitably a population-based LDCT lung cancer screening could become accessible to the eligible high-risk ever-smoker population in Italy. Indeed, whilst evidence from established colorectal, cervical and breast cancer screening programs reveal encouraging participation rates overall (77%, 89% and 84%, respectively), stark regional differences preponderate (74). National statistics indicate a clear north-south gradient, whereby adherence among the southern population lags gravely behind its northern counterpart, with respect to both colorectal (44 *vs.* 98%) and breast (59 *vs.* 98%) cancer screening (74). Acknowledging the health disparities engendered by this divide may offer avenue and justification for future infrastructural investments needed – especially those pertaining to medical devices – in order to ensure that this, and other mass screening programs, reach the intended national scale *equitably* across regions.

Our model has important limitations to highlight. First, the perspective through which we chose to evaluate the cost-effectiveness of the screening intervention does not include indirect costs (*i.e.* those related to time-off work and reduced productivity). Considering the epidemiology of lung cancer in Italy and the fact that those primarily afflicted by the disease tend to fall within working-age (75,76), expanding the perspective beyond the health budget holder is advisable as early detection through screening may lead to considerable additional benefits at societal level (15). Second, our model does not account for the screening participants' cumulative exposure to radiation resulting from the LDCT procedure and its potential effect on future health outcomes. Previous research has deepened our understanding of the radiation carcinogenesis process, evaluating that, though small, the individual risk of radiation-induced malignancy from CT is real and could become significant at the population level (68). Indeed, an annual LDCT screening intervention over 15 years could result in a cumulative radiation exposure of 22.5 mSv per patient (14), yet recent evidence synthesis suggests that the impending benefits of lung cancer screening far outweigh the potential detriment incurred by increased exposure to radiation (77). Third, our model assumes that the

Italian high-risk ever-smoker population shares a homogenous heavy-smoking profile. In this regard, we are unable to differentiate the risk of developing lung cancer, as well as the speed of tumour growth, between ever-smokers with varying durations of heavy smoking habits and cessation times in the eligible screening cohort. Thus, our base case estimates should be interpreted with caution, as our ICERs may depend on the underlying assumption of homogeneity of risk properties across the cohort. Nonetheless, deviations from the base case probability to transition from no lung cancer to stages I and II, and their influence on the ICERs, were likely captured within our sensitivity analyses. Deterministic and probabilistic changes to the parameter denoting lung cancer incidence, which would be most affected by the assumption of a homogenous risk profile, convey robustness of the cost-effectiveness estimate.

Overall, our modelling study for the Italian context reveals that population-based LDCT lung cancer screening is cost-effective for a number of different screening invitation scenarios. Our findings offer robust support for policy makers, payers and guideline developers who are faced with the important decision of whether to implement population-based, life-saving, lung cancer screening programs. Moreover, we provide evidence that the comparative effectiveness of different invitation strategies intended to improve engagement with the high-risk population of ever smokers generates sufficient variation in uptake so as to increase the cost-effectiveness of strategies.

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Table 1. Transition probabilities for the natural history model component (usual care scenario)

	Base-case value	Distribution	Reference
No lung cancer to:			
No lung cancer	0.99138	Dirichlet (based on beta)	Model calibration (ISTAT 2017a; b)
Stage I	0.00550	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage II	3.00E-08	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.00312	Dirichlet (based on beta)	Model calibration (ISTAT 2017a; b)
Stage I lung cancer to:			
Stage I	0.47550	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage II	0.20580	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIA	0.02280	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIB	1.00E-08	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.11690	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.02460	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.15440	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage II lung cancer to:			
Stage II	0.25990	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIA	0.27800	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIB	0.05000	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.23900	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.05000	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.12310	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage IIIA lung cancer to:			
Stage IIIA	0.33610	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIB	0.22460	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.20550	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.08110	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.15270	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage IIIB lung cancer to:			
Stage IIIB	0.26340	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.03360	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.51770	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.18530	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage IV lung cancer to:			
Stage IV	0.09380	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.60840	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.29780	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)

Sources:

Detterbeck, F.C. and Gibson, C.J., 2008. Turning grey: the natural history of lung cancer over time. Journal of Thoracic Oncology, 3(7), pp.781-792.

Hofer, F., Kauczor, H.U. and Stargardt, T., 2018. Cost-utility analysis of a potential lung cancer screening program for a high-risk population in Germany: a modelling approach. Lung Cancer, 124, pp.189-198.

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ISTAT, 2017b. Resident Population Database [Internet]. [cited 2020 September 15]. Available from: http://dati.istat.it/

Table 2. Transition probabilities for the natural history model component (scenarios with LDCT-LCS)

	Base-case value	Distribution	Reference
No lung cancer to:			
No lung cancer	0.99138	Dirichlet (based on beta)	Model calibration (ISTAT 2017a; b)
Stage I	0.00550	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage II	0.00000	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Death	0.00312	Dirichlet (based on beta)	Model calibration (ISTAT 2017a; b)
Stage I lung cancer to:			
Stage I	0.42285	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage II	0.18301	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIA	0.02028	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIB	0.00000	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.10396	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.13259	Dirichlet (based on beta)	Model calibration (ten Haaf 2015)
Death	0.13731	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage II lung cancer to:			
Stage II	0.23352	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIA	0.24978	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIB	0.04492	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.21474	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.14644	Dirichlet (based on beta)	Model calibration (ten Haaf 2015)
Death	0.11060	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage IIIA lung cancer to:			
Stage IIIA	0.27270	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IIIB	0.18223	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.16674	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.25443	Dirichlet (based on beta)	Model calibration (ten Haaf 2015)
Death	0.12390	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage IIIB lung cancer to:			
Stage IIIB	0.37784	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Stage IV	0.04820	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.30816	Dirichlet (based on beta)	Model calibration (ten Haaf 2015)
Death	0.26581	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)
Stage IV lung cancer to:			
Stage IV	0.09214	Dirichlet (based on beta)	Model calibration (Pegna 2013)
Diagnosis	0.61531	Dirichlet (based on beta)	Model calibration (ten Haaf 2015)
Death	0.29255	Dirichlet (based on beta)	Model calibration (Detterbeck 2008)

Sources:

Detterbeck, F.C. and Gibson, C.J., 2008. Turning gray: the natural history of lung cancer over time. Journal of Thoracic Oncology, 3(7), pp.781-792.

Hofer, F., Kauczor, H.U. and Stargardt, T., 2018. Cost-utility analysis of a potential lung cancer screening program for a high-risk population in Germany: a modelling approach. Lung Cancer, 124, pp.189-198.

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Table 3. Treatment distribution per lung cancer stage

	Base-case value	Distribution	Reference
Stage I lung cancer to:			
Surgery	0.9	Dirichlet (based on beta)	Pegna 2013
Surgery + Chemo	0.05	Dirichlet (based on beta)	Pegna 2013
Surgery + Chemo + Radio	0.05	Dirichlet (based on beta)	Pegna 2013
Stage II lung cancer to:			
Surgery + Chemo	0.8	Dirichlet (based on beta)	Pegna 2013
Surgery + Chemo + Radio	0.2	Dirichlet (based on beta)	Pegna 2013
Stage IIIA lung cancer to:			
Surgery + Chemo + Radio	0.2	Dirichlet (based on beta)	Pegna 2013
Chemo + Radio	0.8	Dirichlet (based on beta)	Pegna 2013
Stage IIIB lung cancer to:			
Chemo + Radio	0.5	Dirichlet (based on beta)	Pegna 2013
Palliative	0.5	Dirichlet (based on beta)	Pegna 2013
Stage IV lung cancer to:			
Palliative	1		Pegna 2013

Source:
Pegna, A.L., Picozzi, G., Falaschi, F., Carrozzi, L., Falchini, M., Carozzi, F.M., Pistelli, F., Comin, C., Deliperi, A., Grazzini, M. and Innocenti, F., 2013. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. Journal of Thoracic Oncology, 8(7), pp.866-875.

Table 4. Transition probabilities for the treatment and aftercare model component

	Base-case value	Distribution	Reference
Surgery to:			
Aftercare I	0.9593	Dirichlet (based on beta)	Goldstraw 2016
Death	0.0407	Dirichlet (based on beta)	Goldstraw 2016
Surgery + Chemo to:			
Aftercare II	0.9562	Dirichlet (based on beta)	Goldstraw 2016
Death	0.0438	Dirichlet (based on beta)	Goldstraw 2016
Surgery + Chemo + Radio to:			
Aftercare III	0.9235	Dirichlet (based on beta)	Goldstraw 2016
Death	0.0765	Dirichlet (based on beta)	Goldstraw 2016
Chemo + Radio to:			
Aftercare IV	0.8948	Dirichlet (based on beta)	Goldstraw 2016
Death	0.1052	Dirichlet (based on beta)	Goldstraw 2016
Palliative to:			
Palliative	0.8584	Dirichlet (based on beta)	Goldstraw 2016
Death	0.1416	Dirichlet (based on beta)	Goldstraw 2016
Aftercare I to:			
Aftercare I	0.9459	Dirichlet (based on beta)	Pisters 2005
Chemo + Radio	0.0053	Dirichlet (based on beta)	Pisters 2005
Palliative	0.0081	Dirichlet (based on beta)	Pisters 2005
Death	0.0407	Dirichlet (based on beta)	Goldstraw 2016
Aftercare II to:			
Aftercare II	0.6978	Dirichlet (based on beta)	Pisters 2005
Chemo + Radio	0.0064	Dirichlet (based on beta)	Pisters 2005
Palliative	0.2520	Dirichlet (based on beta)	Pisters 2005
Death	0.0438	Dirichlet (based on beta)	Goldstraw 2016
Aftercare III to:			
Aftercare III	0.8706	Dirichlet (based on beta)	Pisters 2005
Chemo + Radio	0.0081	Dirichlet (based on beta)	Pisters 2005
Palliative	0.0448	Dirichlet (based on beta)	Pisters 2005
Death	0.0765	Dirichlet (based on beta)	Goldstraw 2016
Aftercare IV to:			
Aftercare IV	0.8419	Dirichlet (based on beta)	Pisters 2005
Chemo + Radio	0.0081	Dirichlet (based on beta)	Pisters 2005
Palliative	0.0448	Dirichlet (based on beta)	Pisters 2005
Death	0.1052	Dirichlet (based on beta)	Goldstraw 2016

Sources:
Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology. 2016 Jan;11(1):39–51.
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Table 5. Dynamic cohort parameters

	Base-case value	Distribution	Reference
Cohort size	444,029	Normal	ISTAT 2019
Starting cohort probabilities			
No lung cancer	0.985	Dirichlet (based on beta)	Pegna 2013
Stage I	0.009	Dirichlet (based on beta)	Pegna 2013
Stage II	0.001	Dirichlet (based on beta)	Pegna 2013
Stage IIIA	0.001	Dirichlet (based on beta)	Pegna 2013
Stage IIIB	0.001	Dirichlet (based on beta)	Pegna 2013
Stage IV	0.003	Dirichlet (based on beta)	Pegna 2013
Cohort entry size (annual)	26,699	Normal	ISTAT 2019
Entry cohort probabilities			
No lung cancer	0.985	Dirichlet (based on beta)	Pegna 2013
Stage I	0.009	Dirichlet (based on beta)	Pegna 2013
Stage II	0.001	Dirichlet (based on beta)	Pegna 2013
Stage IIIA	0.001	Dirichlet (based on beta)	Pegna 2013
Stage IIIB	0.001	Dirichlet (based on beta)	Pegna 2013
Stage IV	0.003	Dirichlet (based on beta)	Pegna 2013

Sources:

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Table 6. Screening parameters

	Base-case value	Distribution	Reference
Screening adherence with:			
Usual invitation by local health authorities	0.575	Beta	Wardle 2016
Personalized invitation with GP endorsement	0.582	Beta	Wardle 2016
Personalized invitation with GP endorsement and telephone call	0.682	Beta	Offman 2014
Personalized invitation with GP endorsement, telephone call and offer of private transport	0.764	Beta	Wang 2016
Screening sensitivity			
Sensitivity Stage I	0.4339	Beta	ten Haaf 2015
Sensitivity Stage II	0.4692	Beta	ten Haaf 2015
Sensitivity Stage IIIA	0.6910	Beta	ten Haaf 2015
Sensitivity Stage IIIB	0.7709	Beta	ten Haaf 2015
Sensitivity Stage IV	0.9781	Beta	ten Haaf 2015
Unnecessary PET scan and biopsies	0.0117	Beta	SMAC data 2020
Proportion of early recalls	0.0971	Beta	SMAC data 2020

Sources:

Offman, J., Myles, J., Ariyanayagam, S., Colorado, Z., Sharp, M., Cruice, M., North, B.V., Shiel, S., Baker, T., Jefferies, R. and Binysh, K., 2014. A telephone reminder intervention to improve breast screening information and access. Public Health, 128(11), pp.1017-1022

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Table 7. Utilities associated with the natural history and treatment and aftercare model components

	Base-case value	Distribution	Reference
Natural history			
No lung cancer	0.891	Beta	Szende 2014
Stage I	0.891	Beta	Szende 2014
Stage II	0.891	Beta	Szende 2014
Stage IIIA	0.825	Beta	Assumption based on Tonge 2019
Stage IIIB	0.772	Beta	Assumption based on Tonge 2019
Stage IV	0.706	Beta	Assumption based on Tonge 2019
Screening			
Disutility for unnecessary PET-guided biopsy	-0.03	Beta	Mahadevia 2003
Treatment and aftercare			
Surgery	0.825	Beta	Sturza 2010
Surgery + Chemo	0.825	Beta	Sturza 2010
Surgery + Chemo + Radio	0.772	Beta	Sturza 2010
Chemo + Radio	0.573	Beta	Sturza 2010
Palliative care	0.573	Beta	Sturza 2010
Aftercare I	0.825	Beta	Sturza 2010
Aftercare II	0.825	Beta	Sturza 2010
Aftercare III	0.772	Beta	Sturza 2010
Aftercare IV	0.573	Beta	Sturza 2010

Sources:

Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung Cancer Screening With Helical Computed Tomography in Older Adult Smokers: A Decision and Cost-effectiveness Analysis. JAMA. 2003 Jan 15;289(3):313.

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Table 8. Costs associated with screening, diagnostic procedures, treatment and aftercare

	Base-case value	Distribution	Reference
Diagnostic procedures			
Diagnosis via clinical presentation			
GP outpatient visit	18.08	Gamma	OMCeO 2015
Chest X-ray	15.49	Gamma	Italian MoH 2013
Sonography (*i.e.* ultrasound scan)	15.49	Gamma	Italian MoH 2013
Contrast-enhanced CT scan	124.11	Gamma	Italian MoH 2013
MRI scan (for staging)	115.80	Gamma	Italian MoH 2013
Bronchoscopy	82.63	Gamma	Italian MoH 2013
Diagnosis via screening program			
Registered nurse (30 minutes)	6.51	Gamma	CNEL 2014; ARAN 2018
Radiology technician (30 minutes)	6.51	Gamma	CNEL 2014; ARAN 2018
Radiologist (30 minutes)	11.28	Gamma	ANNAO ASSOMED 2016
LDCT scan	77.67	Gamma	Italian MoH 2013
Pulmonologist (30 minutes)	11.28	Gamma	ANNAO ASSOMED 2016
PET-guided biopsy	66.36	Gamma	Italian MoH 2013
Screening invitation strategies (IS)			
IS1: Usual invitation			
Administrative lump sum	30.00	Gamma	Hofer 2018
Invitation letter postage	2.00	Gamma	Lew 2017
IS2: GP endorsed invitation			
Administrative lump sum	45.00	Gamma	Assumption based on Offman 2014
Personalized letter postage	2.00	Gamma	Lew 2017
IS3: GP endorsement + Telephone call			
Administrative lump sum	45.00	Gamma	Assumption based on Offman 2014
Personalized letter postage	2.00	Gamma	Lew 2017
Caller training	0.05	Gamma	Assumption based on Offman 2014
Caller (10 minutes)	1.56	Gamma	Assumption based on Offman 2014

Table 8. (continued)

	Base-case value	Distribution	Reference
IS4: GP endorsement + Telephone call + Transport			
Administrative lump sum	45.00	Gamma	Assumption based on Offman 2014
Personalized letter and postage	2.00	Gamma	Lew 2017
Caller training	0.05	Gamma	Assumption based on Offman 2014
Caller (10 minutes)	1.56	Gamma	Assumption based on Offman 2014
Offer of private transport	20.00	Gamma	Assumption based on UNC 2015
Treatment and aftercare			
Surgery	14,400.00	Gamma	Schwarzkopf 2015
Surgery + Chemotherapy	20,450.00	Gamma	Schwarzkopf 2015
Surgery + Chemotherapy + Radiotherapy	26,000.00	Gamma	Schwarzkopf 2015
Chemotherapy + Radiotherapy	21,300.00	Gamma	Schwarzkopf 2015
Palliative care	6,300.00	Gamma	Schwarzkopf 2015
Aftercare	100.00	Gamma	Assumption

Sources:

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Table 9. Base-case cost-effectiveness analysis results

	Cost (€)	Incremental Cost (in €)	Effectiveness (QALYs)	Incremental Effectiveness (in QALYs)	ICER (€/QALY)	NMB	Cost-Effectiveness
Dynamic cohort (n=444,029)							
Strategy *(Excluding dominated)*							
Usual care	2,175,363,043		22,812,676			682,204,914,444	95.36
LDCT-LCS with Invitation Strategy 1	2,946,737,294	771,374,251	22,864,817	52,141	14,794	682,997,766,855	128.88
LDCT-LCS with Invitation Strategy 3	3,217,517,801	270,780,507	22,879,777	14,961	18,100	683,175,801,391	140.63
LDCT-LCS with Invitation Strategy 4	3,501,627,551	284,109,750	22,893,912	14,135	20,100	683,315,737,443	152.95
Strategy *(All, referencing common baseline)*							
Usual care	2,175,363,043		22,812,676			682,204,914,444	95.36
LDCT-LCS with Invitation Strategy 1	2,946,737,294	771,374,251	22,864,817	52,141	14,794	682,997,766,855	128.88
LDCT-LCS with Invitation Strategy 2	3,051,334,643	875,971,600	22,865,695	53,019	16,522	682,919,506,304	133.45
LDCT-LCS with Invitation Strategy 3	3,217,517,801	1,042,154,758	22,879,777	67,101	15,531	683,175,801,391	140.63
LDCT-LCS with Invitation Strategy 4	3,501,627,551	1,326,264,508	22,893,912	81,236	16,326	683,315,737,443	152.95
Closed cohort (average individual)							
Strategy *(Excluding dominated)*							
Usual care	3,252.15		36.20			720,680	89.85
LDCT-LCS with Invitation Strategy 1	4,470.83	1,218.68	36.28	0.08	14,527	721,139	123.23
LDCT-LCS with Invitation Strategy 3	4,899.04	428.21	36.30	0.02	17,793	721,192	134.94
LDCT-LCS with Invitation Strategy 4	5,348.50	449.46	36.33	0.02	19,768	721,197	147.23
Strategy *(All, referencing common baseline)*							
Usual care	3,252.15		36.20			720,680	89.85
LDCT-LCS with Invitation Strategy 1	4,470.83	1,218.68	36.28	0.08	14,527	721,139	123.23
LDCT-LCS with Invitation Strategy 2	4,636.77	1,384.62	36.28	0.09	16,232	721,001	127.80
LDCT-LCS with Invitation Strategy 3	4,899.04	1,646.89	36.30	0.11	15,255	721,192	134.94
LDCT-LCS with Invitation Strategy 4	5,348.50	2,096.35	36.33	0.13	16,040	721,197	147.23

Table 10. Resource consumption across usual care and screening scenarios, frequency over 15 years

		Screening cohorts			
	Usual care cohort	Invitation 1 (57.5% adhere)	Invitation 2 (58.2% adhere)	Invitation 3 (68.2% adhere)	Invitation 4 (76.4% adhere)
Diagnostic and screening procedures					
Diagnosis via clinical presentation	74,435	56,966	56,681	52,159	47,702
LDCT screening sessions		5,972,822	6,075,098	7,723,635	9,393,338
PET-guided biopsies		39,566	40,226	50,802	61,372
Unnecessary PET-guided biopsies		17,019	17,310	22,011	26,774
Treatments					
Surgery	7,012	12,705	12,800	14,335	15,875
Surgery + Chemotherapy	3,884	5,283	5,306	5,671	6,032
Surgery + Chemotherapy + Radiotherapy	2,025	2,847	2,861	3,073	3,283
Chemotherapy + Radiotherapy	9,340	10,000	10,010	10,174	10,331
Palliative care (number of patients)	58,954	57,720	57,700	57,371	57,043

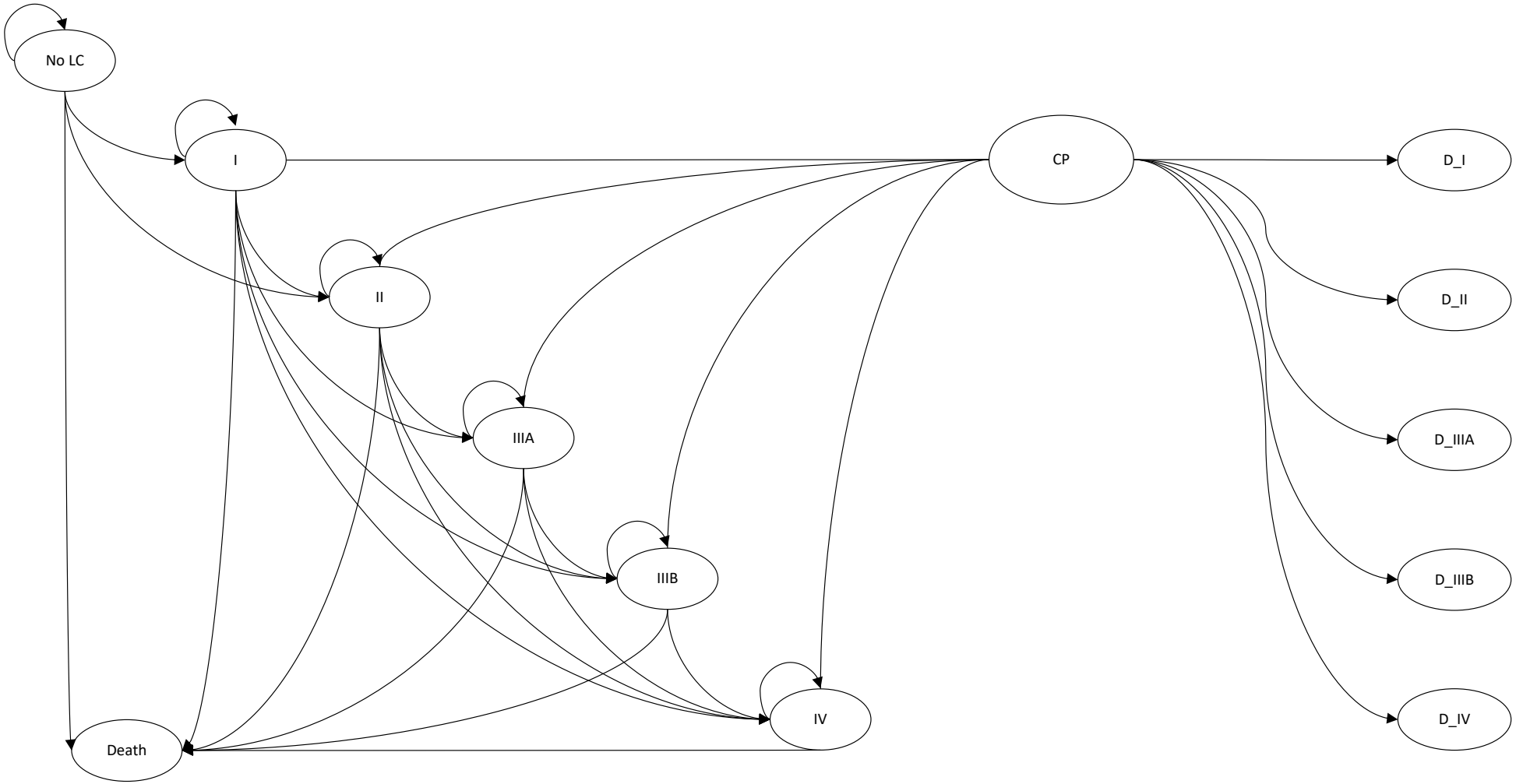
Table 11. Deterministic sensitivity analysis results for dynamic cohort model across undominated strategies (n=444,029)

	Cost (€)	Incremental Cost (in €)	Effectiveness (QALYs)	Incremental Effectiveness (in QALYs)	ICER (€/QALY)	NMB	Cost-Effectiveness
Base-case							
Usual care	2,175,363,043		22,812,676			682,204,914,444	95.36
LDCT-LCS with Invitation Strategy 1	2,946,737,294	771,374,251	22,864,817	52,141	14,794	682,997,766,855	128.88
LDCT-LCS with Invitation Strategy 3	3,217,517,801	270,780,507	22,879,777	14,961	18,100	683,175,801,391	140.63
LDCT-LCS with Invitation Strategy 4	3,501,627,551	284,109,750	22,893,912	14,135	20,100	683,315,737,443	152.95
Assuming 100% increase in LDCT-LCS program costs (€203.94)							
Usual care	2,175,363,043		22,812,676			682,204,914,444	95.36
LDCT-LCS with Invitation Strategy 1	3,433,960,170	1,258,597,127	22,864,817	52,141	24,138	682,510,543,979	150.19
LDCT-LCS with Invitation Strategy 3	3,847,561,413	413,601,244	22,879,777	14,961	27,646	682,545,757,778	168.16
LDCT-LCS with Invitation Strategy 4	4,267,875,824	420,314,411	22,893,912	14,135	29,736	682,549,489,170	186.42
Assuming 50% decrease in LDCT sensitivity of Stage I LC (21.7%)							
Usual care	2,175,363,043		22,812,676			682,204,914,444	95.36
LDCT-LCS with Invitation Strategy 1	2,923,517,924	748,154,880	22,844,579	31,903	23,451	682,413,847,715	127.97
LDCT-LCS with Invitation Strategy 3	3,188,118,256	264,600,333	22,853,836	9,257	28,584	682,426,958,514	139.50
LDCT-LCS with Invitation Strategy 4	3,466,596,762	278,478,505	22,862,625	8,789	31,685	682,412,148,005	151.63
Assuming a 50% decrease in the probability of progression to Stage I LC (0.00275)							
Usual care	1,257,022,514		23,960,855			717,568,622,131	52.46
LDCT-LCS with Invitation Strategy 1	2,031,504,446	774,481,931	23,995,881	35,027	22,111	717,844,936,534	84.66
LDCT-LCS with Invitation Strategy 3	2,306,276,601	274,772,155	24,005,970	10,088	27,237	717,872,810,556	96.07
LDCT-LCS with Invitation Strategy 4	2,595,887,105	289,610,504	24,015,517	9,547	30,334	717,869,623,337	108.09

Table 11. (continued)

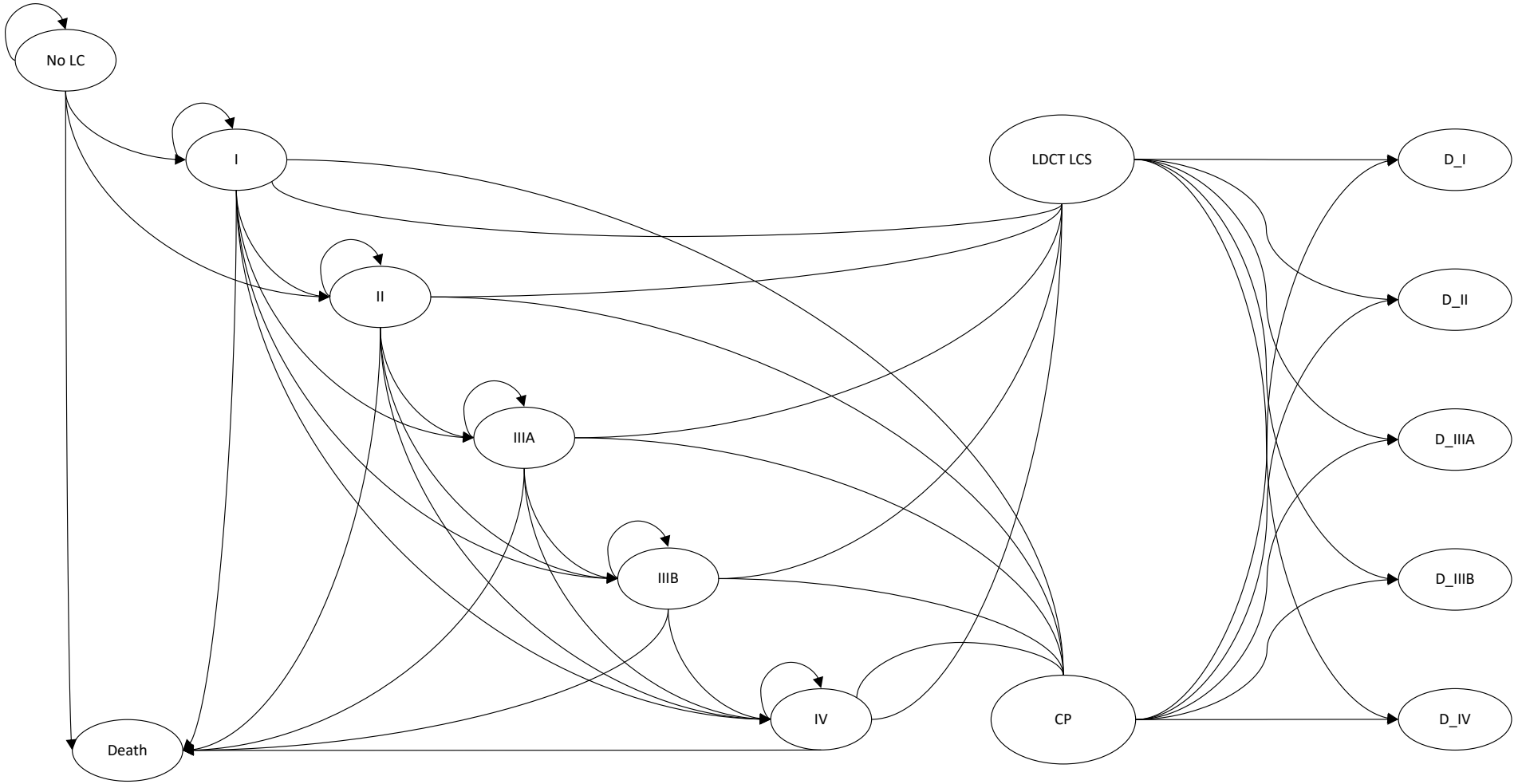
	Cost (€)	Incremental Cost (in €)	Effectiveness (QALYs)	Incremental Effectiveness (in QALYs)	ICER (€/QALY)	NMB	Cost-Effectiveness
Assuming a 200% increase in cohort size (n=1,332,087)							
Usual care	5,292,702,655		54,544,334			1,631,037,331,460	97.03
LDCT-LCS with Invitation Strategy 1	7,136,868,012	1,844,165,356	54,673,275	128,941	14,302	1,633,061,385,590	130.54
LDCT-LCS with Invitation Strategy 3	7,784,187,374	647,319,362	54,710,261	36,986	17,502	1,633,523,645,320	142.28
LDCT-LCS with Invitation Strategy 4	8,463,352,061	679,164,687	54,745,202	34,941	19,438	1,633,892,696,913	154.60
Limiting the model time horizon to 10 years							
Usual care	1,396,997,902		15,801,142			472,637,274,897	88.41
LDCT-LCS with Invitation Strategy 1	1,926,430,832	529,432,930	15,831,768	30,626	17,287	473,026,615,751	121.68
LDCT-LCS with Invitation Strategy 3	2,112,642,882	186,212,049	15,840,568	8,799	21,162	473,104,382,456	133.37
LDCT-LCS with Invitation Strategy 4	2,308,188,842	195,545,961	15,848,886	8,319	23,507	473,158,395,429	145.64

Figure 1. Markov model component depicting the natural progression of lung cancer and possible transitions in a scenario where diagnosis occurs via usual care



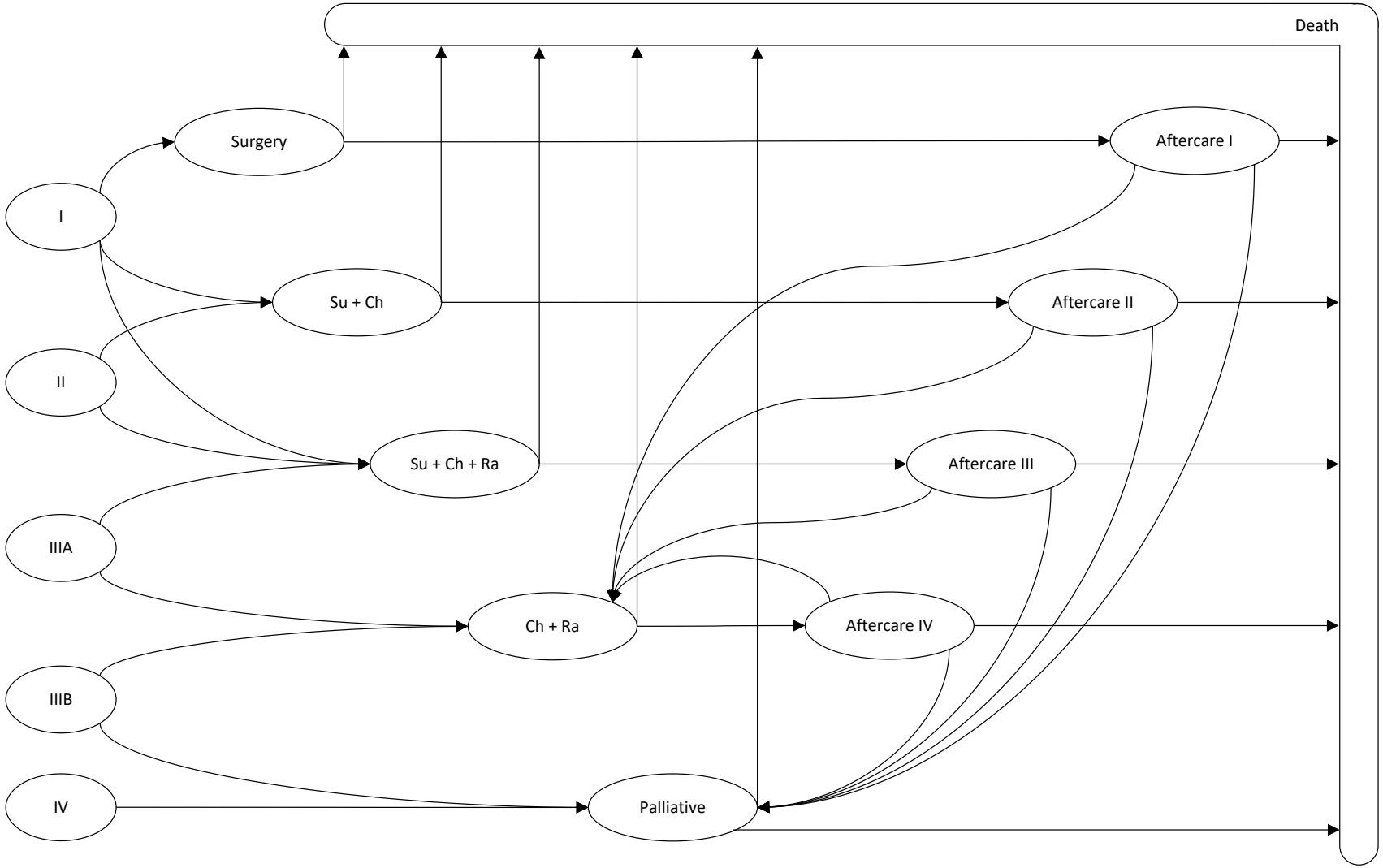
LC: Lung cancer
CP: Clinical presentation
D: Diagnosed

Figure 2. Markov model component depicting the natural progression of lung cancer and possible transitions in scenarios where diagnosis occurs via LDCT-LCS



LC: Lung cancer
LDCT: Low dose computed tomography
LCS: Lung cancer screening
CP: Clinical presentation
D: Diagnosed

Figure 3. Markov model component depicting the treatment and aftercare paths depending on stage at lung cancer diagnosis



Su: Surgery
Ch: Chemotherapy
Ra: Radiotherapy

Figure 4. LDCT screening algorithm

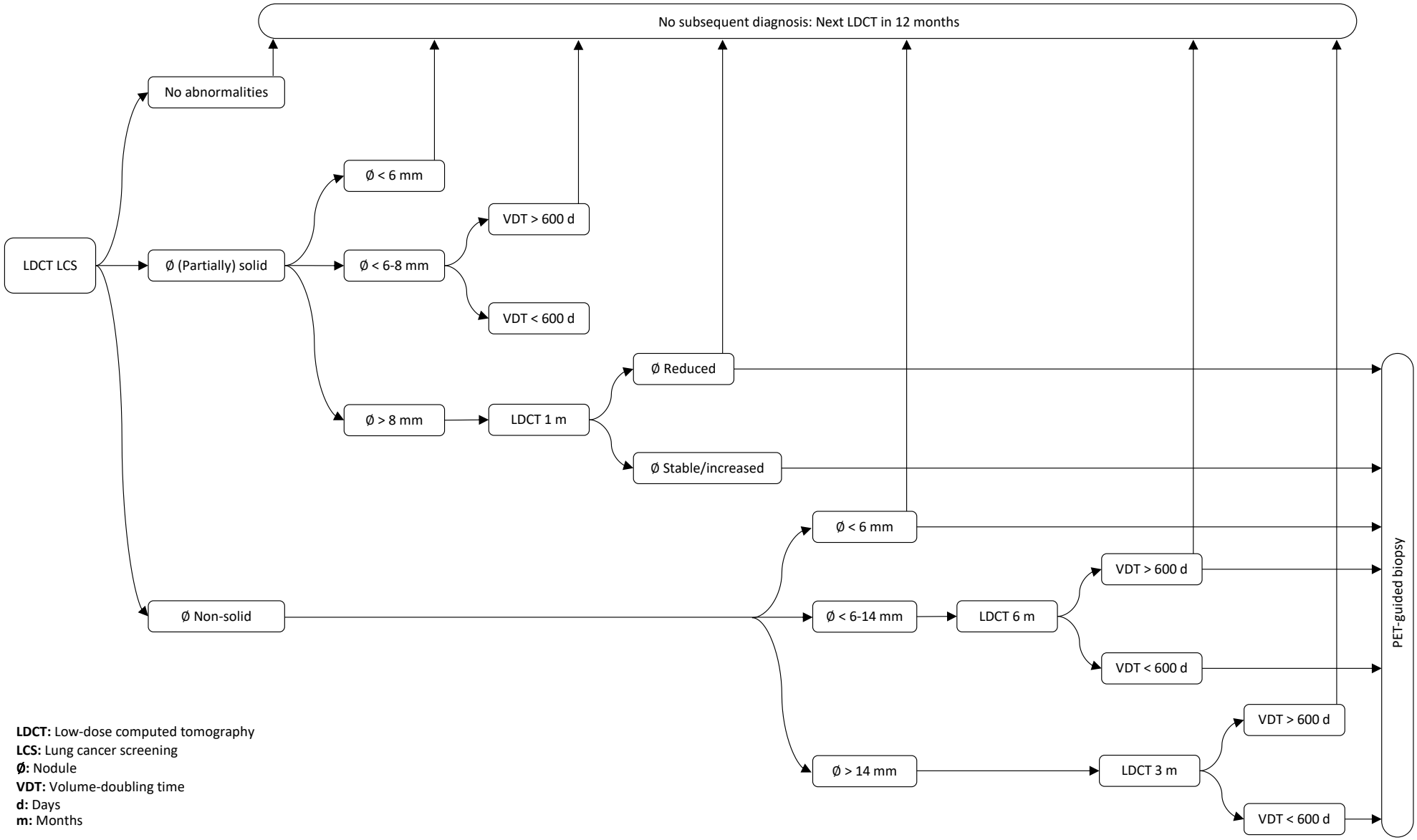


Figure 5. Incremental cost-effectiveness

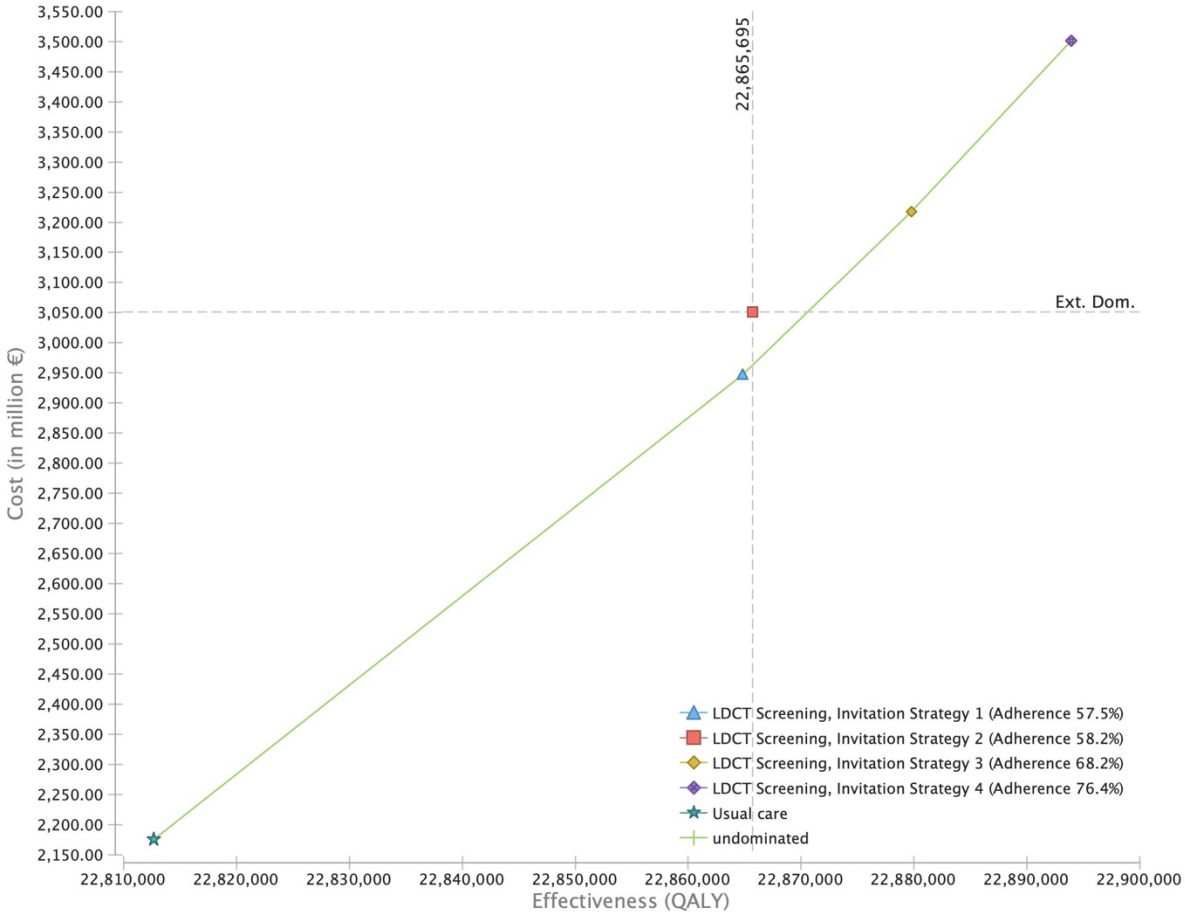
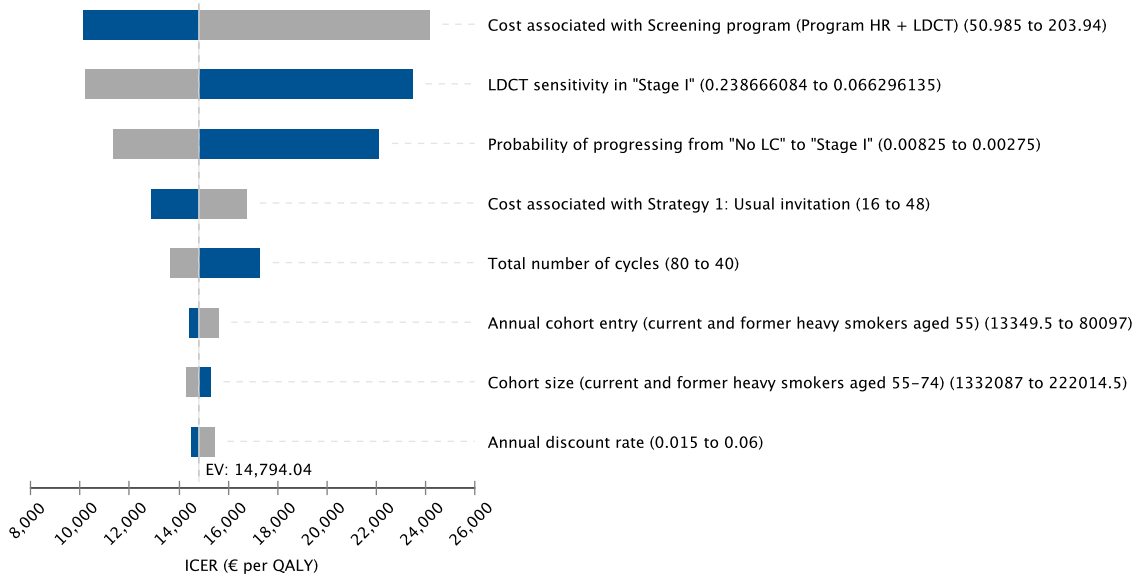
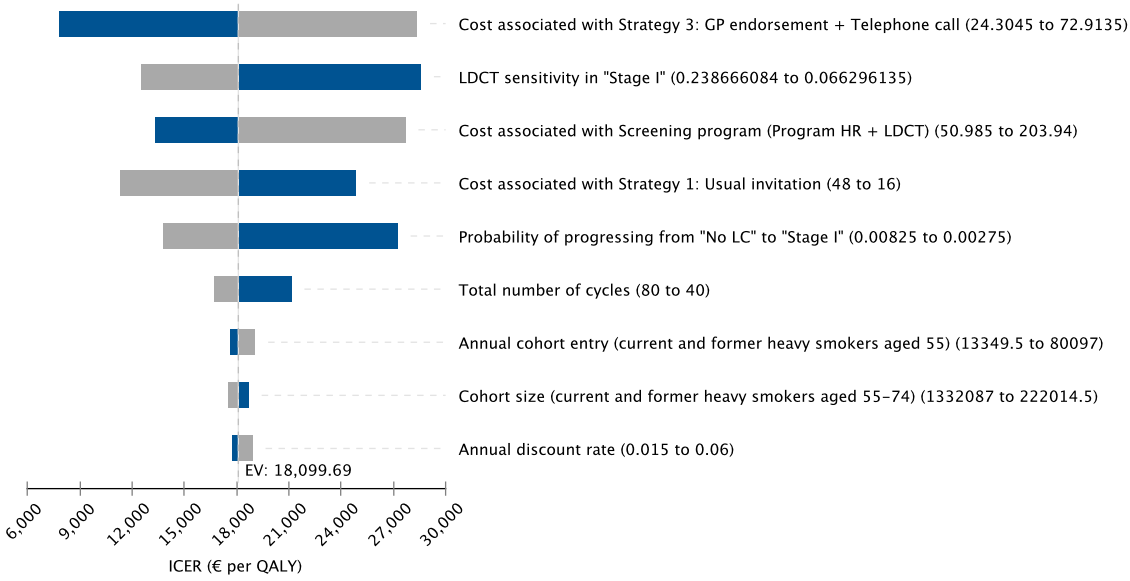


Figure 6. Tornado plots: (A) LDCT screening with invitation strategy 1 vs. Usual care, (B) LDCT screening with invitation strategy 3 vs. 1, (C) LDCT screening with invitation strategy 4 vs. 3

A.



B.



C.

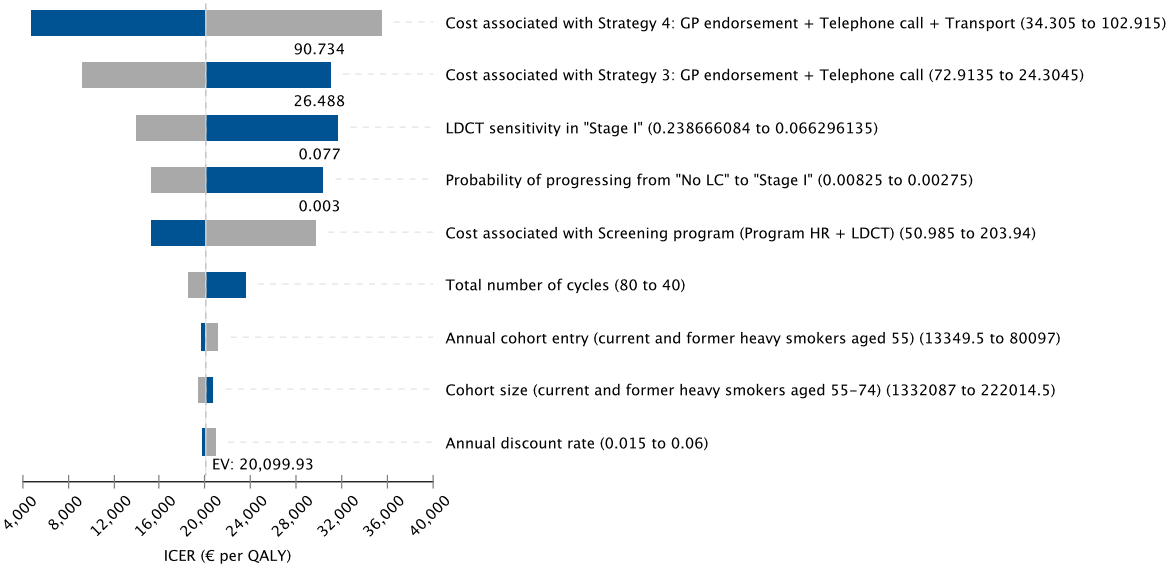


Figure 7. Incremental cost-effectiveness scatter plot, Monte Carlo simulation results after 10,000 draws: (A) LDCT screening with invitation strategy 1 vs. Usual care, (B) LDCT screening with invitation strategy 3 vs. Usual care, (C) LDCT screening with invitation strategy 4 vs. Usual care

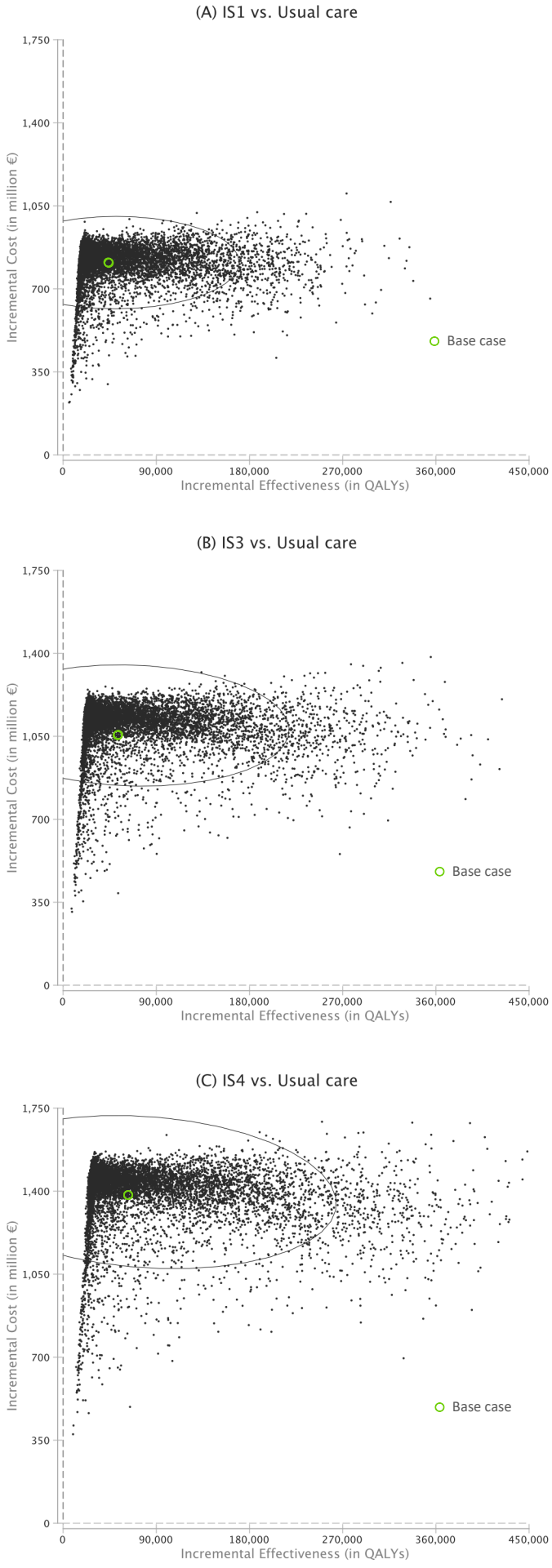


Figure 8. Incremental cost-effectiveness scatter plot, Monte Carlo simulation results after 10,000 draws: (A) LDCT screening with invitation strategy 1 vs. Usual care, (B) LDCT screening with invitation strategy 3 vs. 1, (C) LDCT screening with invitation strategy 4 vs. 3

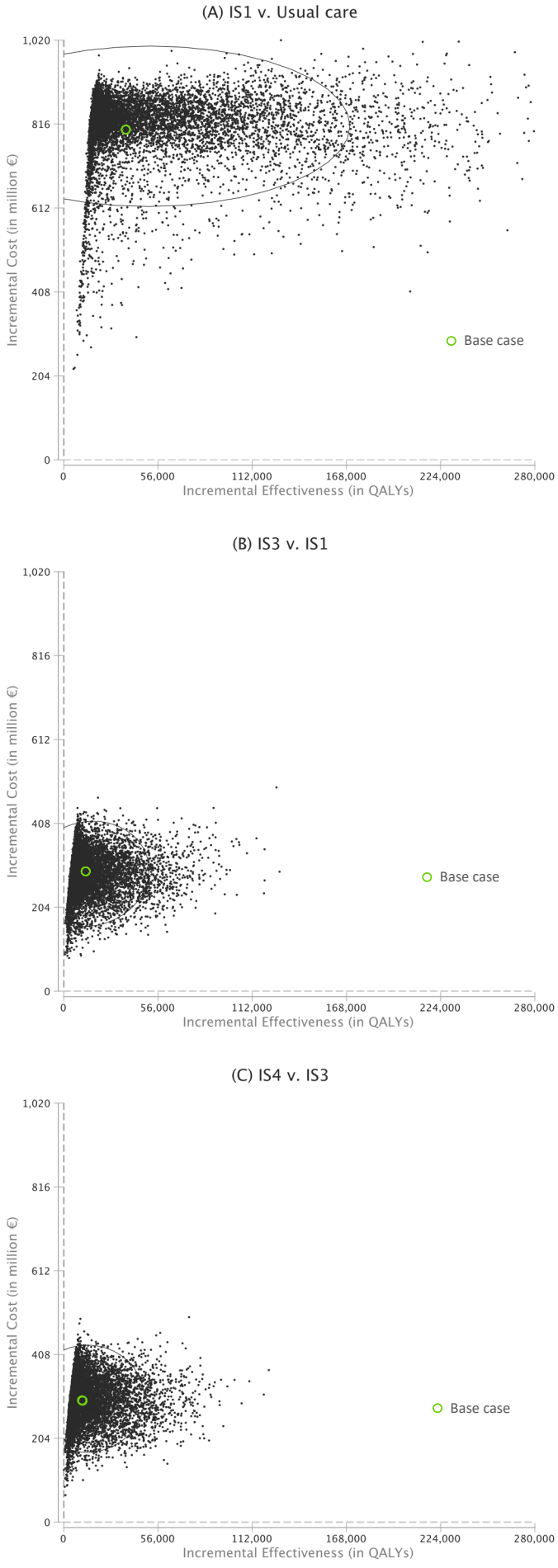


Figure 9. Cost-effectiveness acceptability curve, Monte Carlo simulation results after 10,000 draws

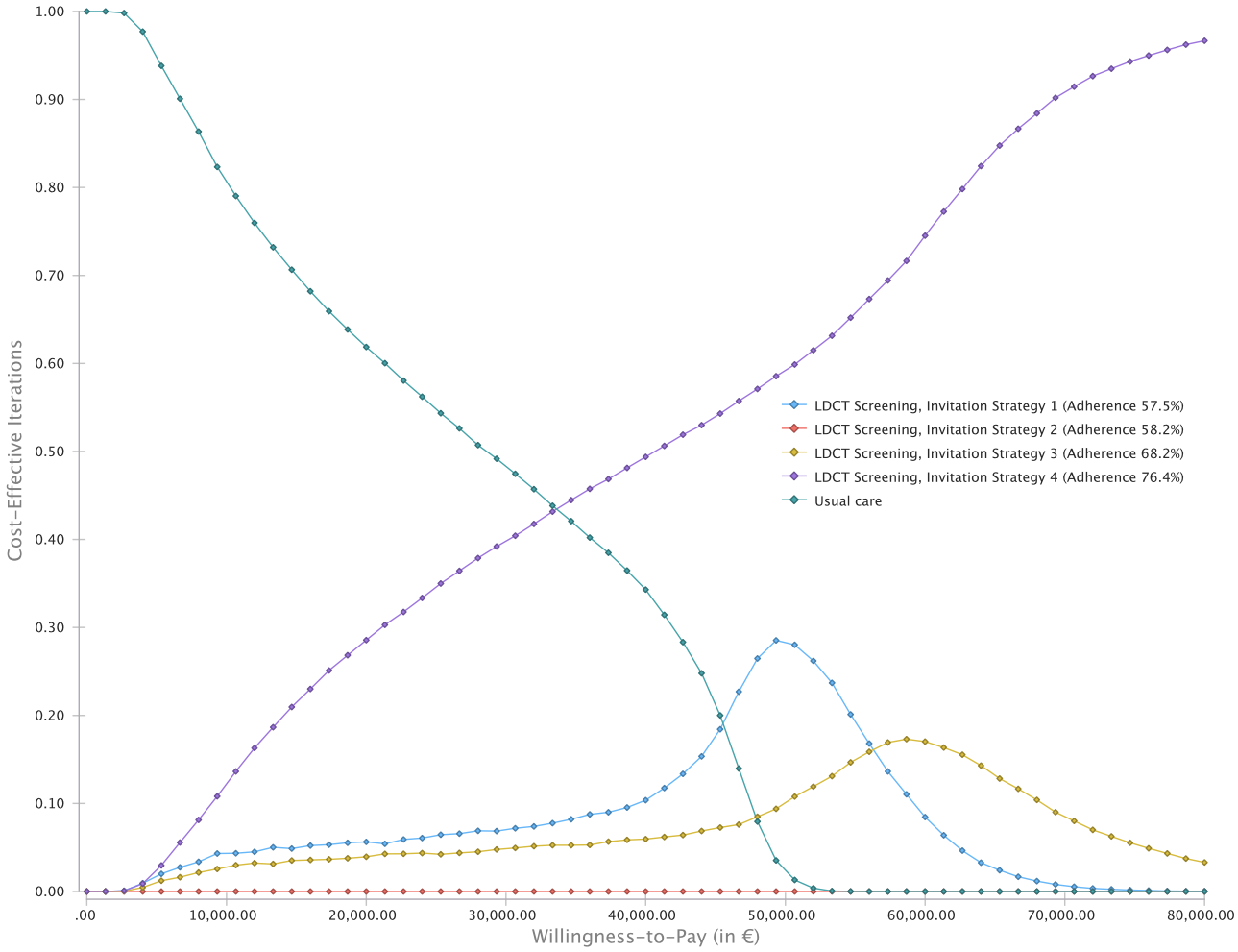


Figure 10. ICER sensitivity to LDCT-LCS adherence across undominated invitation strategies, compared to the usual care scenario

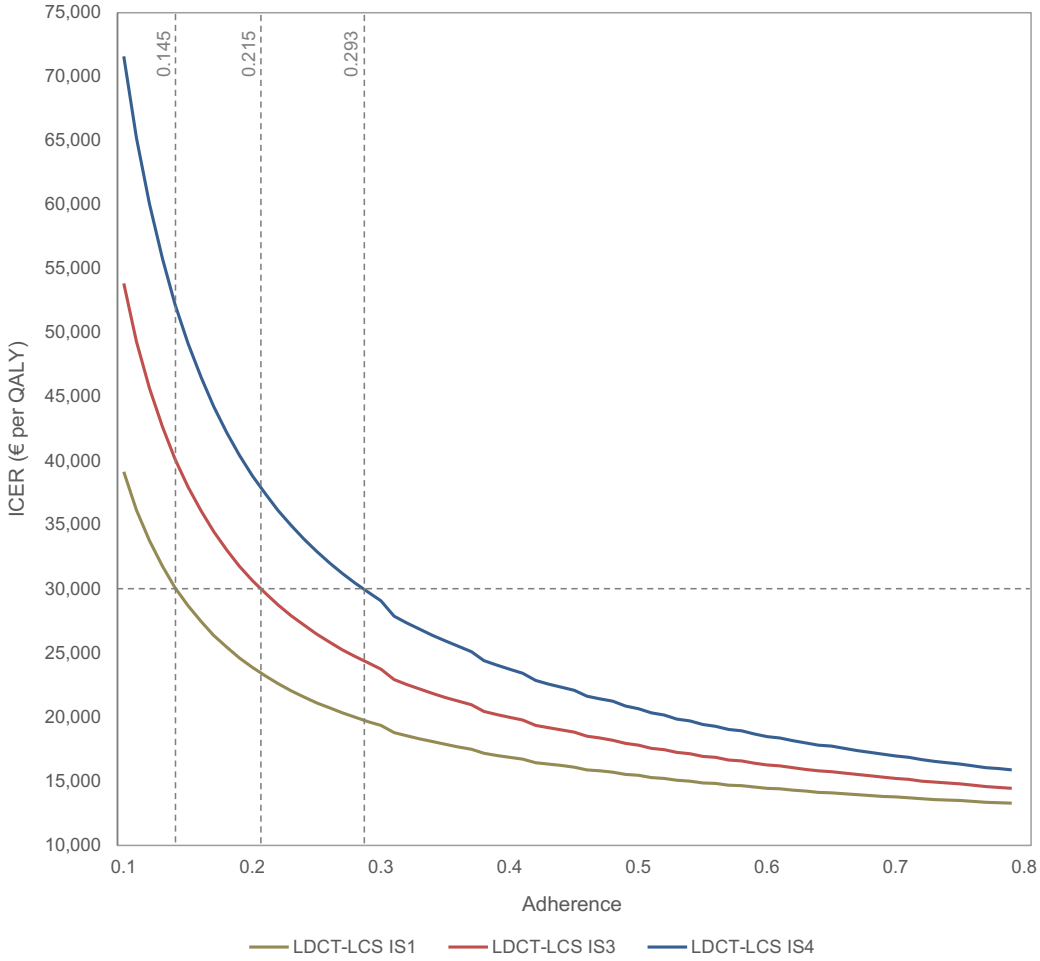
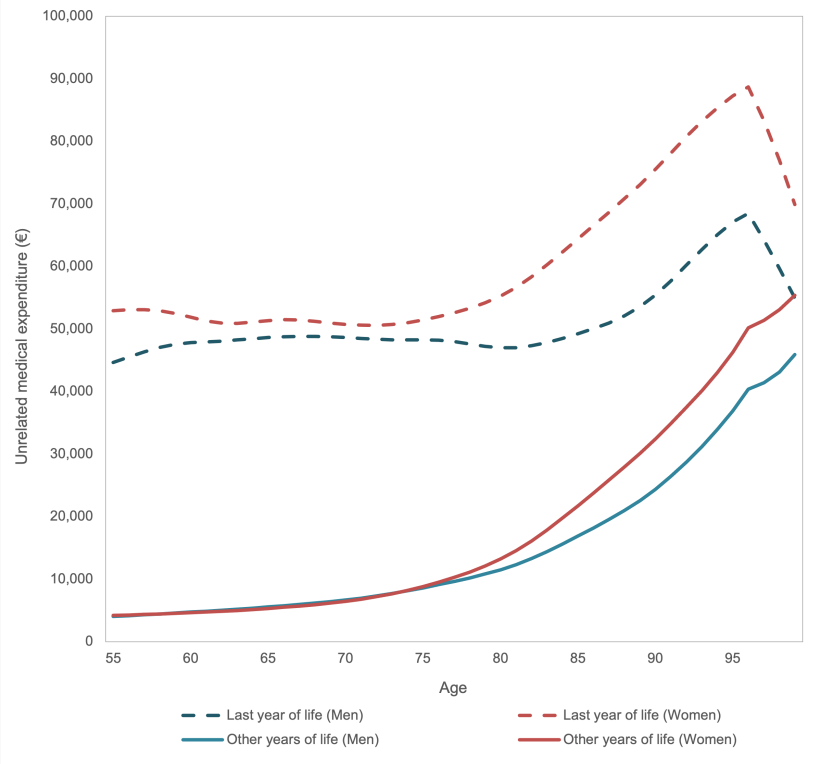
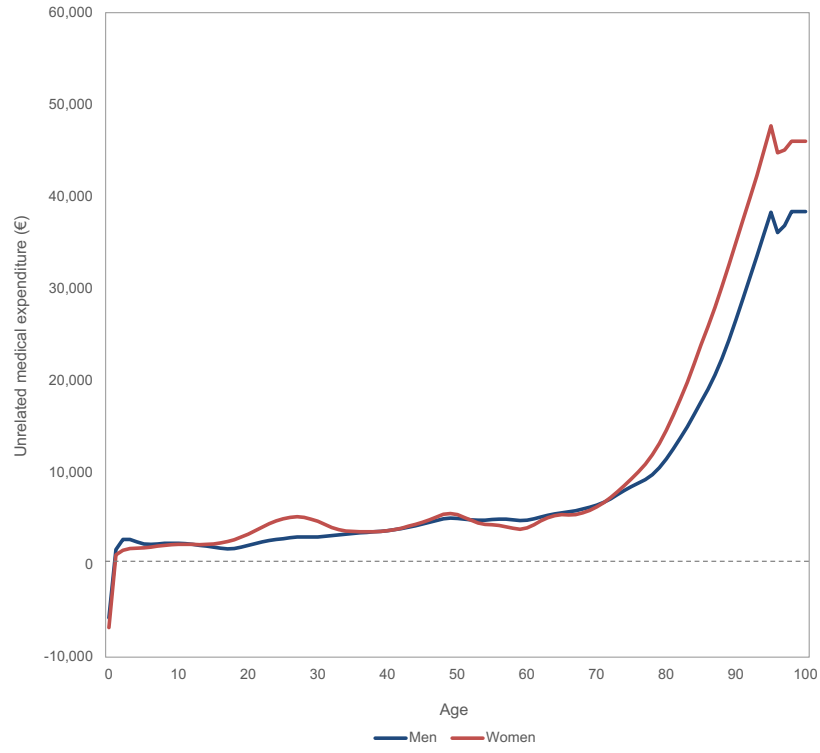


Figure 11. Per capita annual health care expenditure for unrelated diseases (top) and per capita annual health care expenditure for unrelated diseases associated with living one additional year (bottom)





Conclusion

The landscape of 'global' health utilization varies across, and even within, countries and health sectors irrespective of payment model or health system, yet the fundamental purpose motivating its study is aimed at overcoming the challenges that prevent better and equitable uptake of effective interventions. This dissertation was fuelled by such purpose. Although each chapter posed a specific utilization question relevant to a unique target population, in its entirety, this work sought to answer the following cross-cutting questions: (i) what are the factors that encourage and challenge utilization of health services, (ii) under which moderating conditions and through which channels is improved utilization supported, and (iii) how can a better understanding of the antecedents of improved utilization contribute to the design of well-targeted, cost-effective health interventions.

In seeking to offer insight into the factors that encourage and challenge utilization, the conditions and channels that sustain it, and the design of programs that may, in turn, be sustained by it, this dissertation positioned health utilization at centre stage. While the experiences of health, infirmity, disability, and mortality are common denominating factors of a shared humanity, the chapters herein exposed distinctive configurations of the 'global' challenges faced by many to receive care. Indeed, the 'global' in global health utilization refers to the scope of an 'all-too-common' human struggle to seek, reach, afford and receive care – *not* its location.

Chapter 1 established the causal effect of health insurance participation on the use of essential health services in Ghana, thereby revealing substantial effect differences across socio-geographic groups. Building on this insight, Chapter 2 examined alternative causal pathways leading to health utilization in India, which incorporate the effect of women's social status, in the form of marital age. Chapter 3 investigated the factors and mediational processes influencing an important antecedent of preventive care-seeking behaviour, contemplation, in a typically hard-to-reach heavy smoker population in Italy. Finally, Chapter 4 built a cost-effectiveness model of a mass targeted cancer screening program, which through the inclusion of invitation-based scenarios, sought to highlight the economic relevance of interventions designed with a view towards improving utilization within high-risk populations.

Together, this dissertation shed light on some of the factors influencing health utilization, while offering economic insight into how utilization-conscious designs may lead to better-targeted programs. We do so with the intention to contribute to the formulation of evidence-based health policies seeking to improve utilization among underserved groups, for whom curative and preventive health services remain beyond reach. Capable of revealing the ways in which our health systems often fail those in need, the field of 'global' health utilization can be galvanized to both understand and transcend the limitations posed by our current systems.