UCL INSTITUTE FOR GLOBAL HEALTH

Research to understand multimorbidity in households affected by tuberculosis

Dr Yohhei Hamada, MD, MPH

PhD Thesis in Global Health

UCL Institute for Global Health

Supervisors:
1. Professor Ibrahim Abubakar, UCL Institute for Global Health
2. Professor Molebogeng X Rangaka, UCL Institute for Global Health

Supervisory team:
Associate Professor Salome Charalambous, Aurum Institute
Professor Andrew Copas, UCL Institute for Global Health
Professor Edward Fottrell, UCL Institute for Global Health
Professor John Hurst, UCL Respiratory
Professor Simon Walker, University of York

Thesis committee:
Chair: Professor Timothy McHugh, Division of Infection & Immunity, UCL
Vice Chair: Dr Matteo Quartagno, MRC-CTU at UCL

I, Yohhei Hamada, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I would like to express my deepest gratitude to the following individuals whose guidance, support, and expertise were invaluable throughout the completion of this thesis.

First and foremost, I am immensely grateful to Professor Ibrahim Abubakar and Professor Molebogeng X Rangaka for providing me with the opportunity to pursue my PhD at UCL. Their unwavering support, insightful feedback, and mentorship greatly enriched my research experience.

I extend my sincere appreciation to my supervisory team for their dedication and guidance throughout this research journey. I would like to thank Professor Andrew Copas for his invaluable statistical guidance, Professor Edward Fottrell and Professor John Hurst for their expertise in non-communicable disease research, and Professor Simon Walker for his guidance in my first health economic research endeavour. Special thanks to Associate Professor Salome Charalambous for allowing me to join the CUT-TB team.

I am grateful to the members of my thesis committee for their time, expertise, and valuable feedback. My heartfelt thanks go to Professor Timothy McHugh for chairing the committee and providing invaluable guidance. I also extend my gratitude to Dr. Matteo Quartagno for serving as the vice-chair and for his valuable input and support in statistical analysis.

My project would not have been possible without access to individual participant data from national prevalence surveys and contact tracing studies. I am extremely grateful to the contributors of my individual participant data meta-analysis, particularly Irwin Law, who facilitated access to national TB prevalence survey data.

I am thankful to my colleagues at UCL and the collaborators of the CUT-TB project who supported me throughout my PhD journey. Special thanks to Anna Tisler, Farihah Malik, and Keolebogile Ntshamane, who served as additional reviewers for my systematic reviews.

Finally, I would like to express my deepest gratitude to my family, Yurie, Sotaro, Taishi, and Hikari. I could not have accomplished this without your unwavering support and encouragement.

Abstract

Background: The syndemic of tuberculosis (TB) and non-communicable diseases (NCD) in low- and middle-income countries (LMIC) threatens lives and livelihoods. I aimed to derive evidence to inform multifaceted interventions for TB and associated multimorbidity in TB-affected households.

Method and Findings: First, I conducted an individual participant data (IPD) meta-analysis of 16 national TB prevalence surveys, revealing a higher smoking prevalence in TB-affected households than in households without TB (odds ratio 1.23; 95% confidence interval [CI]: 1.11-1.38, adjusted for age and gender).

Second, analysis using the same data suggested that current smokers and people with self-reported diabetes were 1.5 times more likely to have prevalent TB, indicating these groups as targets for TB screening.

Third, I conducted an IPD meta-analysis of contact tracing studies to address data gaps in prevalence surveys. Data from 14 studies suggested underdiagnosis of diabetes among household contacts, with scarce data on other NCDs, indicating the need for a prospective clinical study.

Fourth, in a pilot cross-sectional study in South Africa and Tanzania, I assessed the burden of select NCDs among TB household contacts through systematic screening, using neighbourhood households as controls. Among contacts, 12.2% and 39.7% had diabetes and hypertension, respectively, with more than half being newly identified. Their prevalence was similar to that of the controls.

Fifth, a decision tree analysis found that adding NCD screening to contact investigations would additionally cost $24,940 per DALY averted. This cost exceeded the cost-effectiveness threshold in South Africa, potentially influenced by limitations of the analytical approach (e.g., restricting to cardiovascular disease outcomes). The analysis further suggests that targeted screening in high-risk groups could improve cost-effectiveness.

Conclusion: The thesis highlights the high prevalence of undiagnosed NCDs among household contacts of TB, notably diabetes, which could be addressed by integrating NCD screening. Future trials should evaluate its impact on clinical outcomes.

Impact statement

Low- and middle-income countries (LMICs) face a dual epidemic of tuberculosis (TB) and non-communicable diseases (NCDs). These conditions share risk factors like smoking, malnutrition, and poverty, leading to multimorbidity affecting individuals and their households. Integrating NCD care into TB household contact tracing offers a potential solution, but data on NCD burden in TB-affected households and the costs of integrated screening are lacking.

This thesis advances our understanding of TB, priority NCD and NCD risk factors in LMIC and informs integrated care models. Through an individual participant data (IPD) meta-analysis of 16 national TB prevalence surveys, the research highlighted a higher smoking prevalence in TB-affected households compared to those without active TB, underscoring the need to address smoking at the household level. This work has been published in PLoS Global Public Health.

Another meta-analysis using the same IPD identified a high proportion of subclinical TB (38.1%) among individuals with prevalent pulmonary TB. It showed that current smokers and people with known diabetes were at around 1.5-fold higher risk for prevalent TB, highlighting the need for national programs to prioritize these individuals for systematic TB screening. The quantitative estimates can also help estimate yields of TB screening when targeting these individuals. This work has been published in eClinicalMedicine.

To address gaps in TB prevalence survey data, specifically limited data on various types of NCD and reliance on self-report, I conducted an IPD meta-analysis of contact tracing studies and a pilot cross-sectional study in South Africa and Tanzania. These studies revealed a high prevalence of undiagnosed hypertension and diabetes among TB households. The cross-sectional study further found a similar NCD burden in the neighbouring community, emphasizing the need for integrated screening targeting TB households and

possibly beyond in communities with high TB burdens. A manuscript reporting the IPD meta-analysis has been published in the Tropical Medicine and International Health. The cross-sectional study was presented at the South African TB conference, and a manuscript has been published in the International Journal of Tuberculosis and Lung Disease Open.

This thesis also reports a cost-effectiveness analysis of integrated NCD and TB screening within TB-affected households using pilot data from South Africa. The work provides insights into optimizing cost-effectiveness through targeted screening strategies for high-risk individuals. This information is valuable for policymakers and researchers designing similar NCD screening programs.

Overall, the thesis highlights the importance of people-centred care addressing TB and household-wide multimorbidity. I organized two webinars inviting national TB program managers and WHO officers to share my research findings. Additionally, I plan to organize a special webinar in early 2025, in collaboration with WHO and researchers from the London School of Hygiene and Tropical Medicine, to discuss recent research on NCD burden in TB-affected households and advocate for person-centred TB screening programs, extending my research reach and potential for influencing public health policy. Finally, building on my research, I plan to develop a multifaceted TB and NCD screening and prevention intervention that will be tested in a trial, further amplifying the impact of my work.

UCL Research Paper Declaration Form
referencing the doctoral candidate's own published work(s)

Please use this form to declare if parts of your thesis are already available in another format, e.g. if data, text, or figures:

- *have been uploaded to a preprint server*
- *are in submission to a peer-reviewed publication*
- *have been published in a peer-reviewed publication, e.g. journal, textbook.*

This form should be completed as many times as necessary. For instance, if you have seven thesis chapters, two of which containing material that has already been published, you would complete this form twice.

1. For a research manuscript that has already been published (if not yet published, please skip to section 2)

a) **What is the title of the manuscript?**

Association of diabetes, smoking, and alcohol use with subclinical-to-symptomatic spectrum of tuberculosis in 16 countries: an individual participant data meta-analysis of national tuberculosis prevalence surveys

b) **Please include a link to or doi for the work**

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00368-1/fulltext

c) **Where was the work published?**

eClinicalMedicine

d) **Who published the work?** (e.g. OUP)

Elsevier

e) **When was the work published?**

September 2023

f) **List the manuscript's authors in the order they appear on the publication**

Yohhei Hamada, Matteo Quartagno, Irwin Law, Farihah Malik, Frank Adae Bonsu, Ifedayo M.O. Adetifa, Yaw Adusi-Poku, Umberto D'Alessandro, Adedapo Olufemi Bashorun, Vikarunnessa Begum, Dina Bisara Lolong, Tsolmon Boldoo, Themba Dlamini, Simon Donkor, Bintari Dwihardiani, Saidi Egwaga, Muhammad N. Farid, Anna Marie Celina G.Garfin, Donna Mae G Gaviola, Mohammad Mushtuq Husain, Farzana Ismail, Mugagga Kaggwa, Deus. V. Kamara, Samuel Kasozi, Kruger Kaswaswa, Bruce Kirenga, Eveline Klinkenberg, Zuweina Kondo, Adebola Lawanson, David Macheque, Ivan Manhiça, Llang Bridget Maama-Maime, Sayoki Mfinanga, Sizulu Moyo, James Mpunga, Thuli Mthiyane, Dyah Erti Mustikawati, Lindiwe Mvusi, Hoa Binh Nguyen, Hai Viet Nguyen, Lamria Pangaribuan, Philip Patrobas, Mahmudur Rahman, Mahbubur Rahman, Mohammed Sayeedur Rahman, Thato Raleting, Pandu Riono, Nunurai Ruswa, Elizeus Rutebemberwa, Mugabe Frank Rwabinumi, Mbazi Senkoro, Ahmad Raihan Sharif, Welile Sikhondze, Charalambos Sismanidis, Tugsdelger Sovd, Turyahabwe Stavia, Sabera Sultana, Oster Suriani, Albertina Martha Thomas, Kristina Tobing, Martie Van der Walt, Simon Walusimbi, Mohammad Mostafa Zaman, Katherine Floyd, Andrew Copas, Ibrahim Abubakar, Molebogeng X Rangaka.

g) **Was the work peer reviewed?**

Yes.

h) **Have you retained the copyright?**

Yes

i) **Was an earlier form of the manuscript uploaded to a preprint server?** (e.g. medRxiv). If 'Yes', please give a link or doi)

No
If 'No', please seek permission from the relevant publisher and check the box next to the below statement:

☒

*I acknowledge permission of the publisher named under **1d** to include in this thesis portions of the publication named as included in **1c**.*

2. **For a research manuscript prepared for publication but that has not yet been published** (if already published, please skip to section 3)

   a) **What is the current title of the manuscript?**

   Click or tap here to enter text.

   b) **Has the manuscript been uploaded to a preprint server?** (e.g. medRxiv; if 'Yes', please give a link or doi)

   Click or tap here to enter text.

   c) **Where is the work intended to be published?** (e.g. journal names)

   Click or tap here to enter text.

   d) **List the manuscript's authors in the intended authorship order**

   Click or tap here to enter text.

   e) **Stage of publication** (e.g. in submission)

   Click or tap here to enter text.

3. **For multi-authored work, please give a statement of contribution covering all authors** (if single-author, please skip to section 4)

   YH, MQ, IA, AC, and MXR designed the study protocol. YH and FM did the systematic review. YH analysed the data with assistance and advice from IL, MQ, IA, AC, and MXR.
   The following authors contributed individual data, data curation, editing, and advisement on the manuscript results: FAB, IMOA, YAP, UDA, AOB, VB, DBL, TB, TD, SD, BD, SE, MNF, KF, AMCGG, DMGG, MMH, FI, MK, DVK, SK, KK, BK, EK, ZK, IL, AL, DM, IM, LBMM, SMf, SMo, JM, TM, DEM, LM, HBN, HVN, LP, PP, MahmR, MahbR, MSR, TR, PR, NR, ER, MFR, MS, ARS, WS, CS, TSo, TSt, SS, OS, AMT, KT, MVDW, SW, and MMZ.
   YH wrote the first draft of the manuscript, which was revised based on comments from co-authors. All authors approved the final version of the manuscript. YH and IL accessed and verified the underlying data, and YH had the final responsibility for the decision to submit it for publication.

4. **In which chapter(s) of your thesis can this material be found?**

   Chapter 3

5. **e-Signatures confirming that the information above is accurate** (this form should be co-signed by the supervisor/ senior author unless this is not appropriate, e.g. if the paper was a single-author work)

Candidate
Yohhei Hamada
Date:
30 April 2024

Supervisor/ Senior Author (where appropriate)
Molebogeng X Rangaka
Date
2 May 2024

UCL Research Paper Declaration Form
referencing the doctoral candidate's own published work(s)

Please use this form to declare if parts of your thesis are already available in another format, e.g. if data, text, or figures:

- *have been uploaded to a preprint server*
- *are in submission to a peer-reviewed publication*
- *have been published in a peer-reviewed publication, e.g. journal, textbook.*

This form should be completed as many times as necessary. For instance, if you have seven thesis chapters, two of which containing material that has already been published, you would complete this form twice.

1. For a research manuscript that has already been published (if not yet published, please skip to section 2)

j) **What is the title of the manuscript?**

Tobacco smoking clusters in households affected by tuberculosis in an individual participant data meta-analysis of national tuberculosis prevalence surveys: Time for household-wide interventions?

k) **Please include a link to or doi for the work**

https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0002596

l) **Where was the work published?**

Plos Global Public Health

m) **Who published the work?** (e.g. OUP)

Plos

n) **When was the work published?**

February 2024

o) **List the manuscript's authors in the order they appear on the publication**

Yohhei Hamada, Matteo Quartagno, Irwin Law, Farihah Malik, Frank Adae Bonsu, Ifedayo M.O. Adetifa, Yaw Adusi-Poku, Umberto D'Alessandro, Adedapo Olufemi Bashorun, Vikarunnessa Begum, Dina Bisara Lolong, Tsolmon Boldoo, Themba Dlamini, Simon Donkor, Bintari Dwihardiani, Saidi Egwaga, Muhammad N. Farid, Anna Marie Celina G.Garfin, Donna Mae G Gaviola, Mohammad Mushtuq Husain, Farzana Ismail, Mugagga Kaggwa, Deus. V. Kamara, Samuel Kasozi, Kruger Kaswaswa, Bruce Kirenga, Eveline Klinkenberg, Zuweina Kondo, Adebola Lawanson, David Macheque, Ivan Manhiça, Llang Bridget Maama-Maime, Sayoki Mfinanga, Sizulu Moyo, James Mpunga, Thuli Mthiyane, Dyah Erti Mustikawati, Lindiwe Mvusi, Hoa Binh Nguyen, Hai Viet Nguyen, Lamria Pangaribuan, Philip Patrobas, Mahmudur Rahman, Mahbubur Rahman, Mohammed Sayeedur Rahman, Thato Raleting, Pandu Riono, Nunurai Ruswa, Elizeus Rutebemberwa, Mugabe Frank Rwabinumi, Mbazi Senkoro, Ahmad Raihan Sharif, Welile Sikhondze, Charalambos Sismanidis, Tugsdelger Sovd, Turyahabwe Stavia, Sabera Sultana, Oster Suriani, Albertina Martha Thomas, Kristina Tobing, Martie Van der Walt, Simon Walusimbi, Mohammad Mostafa Zaman, Katherine Floyd, Andrew Copas, Ibrahim Abubakar, Molebogeng X Rangaka

p) **Was the work peer reviewed?**

Yes.

q) **Have you retained the copyright?**

Yes

r) **Was an earlier form of the manuscript uploaded to a preprint server?** (e.g. medRxiv). If 'Yes', please give a link or doi)

No

If 'No', please seek permission from the relevant publisher and check the box next to the below statement:

☒

*I acknowledge permission of the publisher named under **1d** to include in this thesis portions of the publication named as included in **1c**.*

2. **For a research manuscript prepared for publication but that has not yet been published** (if already published, please skip to section 3)

f) **What is the current title of the manuscript?**

Click or tap here to enter text.

g) **Has the manuscript been uploaded to a preprint server?** (e.g. medRxiv; if 'Yes', please give a link or doi)

Click or tap here to enter text.

h) **Where is the work intended to be published?** (e.g. journal names)

Click or tap here to enter text.

i) **List the manuscript's authors in the intended authorship order**

Click or tap here to enter text.

j) **Stage of publication** (e.g. in submission)

Click or tap here to enter text.

3. **For multi-authored work, please give a statement of contribution covering all authors** (if single-author, please skip to section 4)

YH, MQ, IA, AC, and MXR designed the study protocol. YH and FM did the systematic review. YH analysed the data with assistance and advice from IL, MQ, IA, AC, and MXR.
The following authors contributed individual data, data curation, editing, and advisement on the manuscript results: FAB, IMOA, YAP, UDA, AOB, VB, DBL, TB, TD, SD, BD, SE, MNF, KF, AMCGG, DMGG, MMH, FI, MK, DVK, SK, KK, BK, EK, ZK, IL, AL, DM, IM, LBMM, SMf, SMo, JM, TM, DEM, LM, HBN, HVN, LP, PP, MahmR, MahbR, MSR, TR, PR, NR, ER, MFR, MS, ARS, WS, CS, TSo, TSt, SS, OS, AMT, KT, MVDW, SW, and MMZ.
YH wrote the first draft of the manuscript, which was revised based on comments from co-authors. All authors approved the final version of the manuscript. YH and IL accessed and verified the underlying data, and YH had the final responsibility for the decision to submit it for publication.

4. **In which chapter(s) of your thesis can this material be found?**

Chapter 4

5. **e-Signatures confirming that the information above is accurate** (this form should be co-signed by the supervisor/ senior author unless this is not appropriate, e.g. if the paper was a single-author work)

Candidate
Yohhei Hamada
Date:
30 April 2024

Supervisor/ Senior Author (where appropriate)
Molebogeng X Rangaka
Date
2 May 2024

UCL Research Paper Declaration Form
referencing the doctoral candidate's own published work(s)

Please use this form to declare if parts of your thesis are already available in another format, e.g. if data, text, or figures:

- *have been uploaded to a preprint server*
- *are in submission to a peer-reviewed publication*
- *have been published in a peer-reviewed publication, e.g. journal, textbook.*

This form should be completed as many times as necessary. For instance, if you have seven thesis chapters, two of which containing material that has already been published, you would complete this form twice.

1. For a research manuscript that has already been published (if not yet published, please skip to section 2)

s) **What is the title of the manuscript?**
Prevalence of non-communicable diseases among household contacts of people with tuberculosis: a systematic review and individual participant data meta-analysis

t) **Please include a link to or doi for the work**
https://onlinelibrary.wiley.com/doi/10.1111/tmi.14038

u) **Where was the work published?**

Tropical Medicine & International Health

v) **Who published the work?** (e.g. OUP)

Wiley

w) **When was the work published?**

July 2024

x) **List the manuscript's authors in the order they appear on the publication**

Yohhei Hamada, Matteo Quartagno, Farihah Malik, Keolebogile Ntshamane, Anna Tisler, Sanjay Gaikwad, Carlos Acuna-Villaorduna, Perumal Kannabiran Bhavani, Bachti Alisjahbana, Katharina Ronacher, Lika Apriani, Mercedes Becerra, Alexander L. Chu, Jacob Creswell, Gustavo Diaz, Beatriz E. Ferro, Jerome T. Galea, Louis Grandjean, Harleen M. S. Grewal, Amita Gupta, Edward C. Jones-López, Léanie Kleynhans, Leonid Lecca, Peter MacPherson, Megan Murray, Diana Marín, Blanca I. Restrepo, Shri Vijay Bala Yogendra Shivakumar, Eileen Shu, Dhanasekaran Sivakumaran, Luan Nguyen Quang Vo, Emily L. Webb, Andrew Copas, Ibrahim Abubakar, Molebogeng X. Rangaka

y) **Was the work peer reviewed?**

Yes.

z) **Have you retained the copyright?**

Yes

aa) **Was an earlier form of the manuscript uploaded to a preprint server?** (e.g. medRxiv). If 'Yes', please give a link or doi)

No

If 'No', please seek permission from the relevant publisher and check the box next to the below statement:

☒

*I acknowledge permission of the publisher named under **1d** to include in this thesis portions of the publication named as included in **1c**.*

2. **For a research manuscript prepared for publication but that has not yet been published** (if already published, please skip to section 3)

   k) **What is the current title of the manuscript?**

   Click or tap here to enter text.

   l) **Has the manuscript been uploaded to a preprint server?** (e.g. medRxiv; if 'Yes', please give a link or doi)

   Click or tap here to enter text.

   m) **Where is the work intended to be published?** (e.g. journal names)

   Click or tap here to enter text.

   n) **List the manuscript's authors in the intended authorship order**

   Click or tap here to enter text.

   o) **Stage of publication** (e.g. in submission)

3. **For multi-authored work, please give a statement of contribution covering all authors** (if single-author, please skip to section 4)

   YH, MQ, IA, AC, and MXR designed the study protocol. YH, FM, KN, and AT did the systematic review. YH analysed the data with assistance and advice from MQ, IA, AC, and MXR.
   The following authors contributed individual data, data curation, editing, and advisement on the manuscript results: SG, CAV, BPK, BA, KR, LA, MB, ALC, JC, GD, BEF, JTG, LG, HMSG, AG, ECJL, LK, LL, PM, MM, DM, BIR, SVBYS, ES, DS, LNQV, ELW.
   YH wrote the first draft of the manuscript, which was revised based on comments from co-authors. All authors approved the final version of the manuscript. YH had the final responsibility for the decision to submit it for publication.

4. **In which chapter(s) of your thesis can this material be found?**

   Chapter 5

5. **e-Signatures confirming that the information above is accurate** (this form should be co-signed by the supervisor/ senior author unless this is not appropriate, e.g. if the paper was a single-author work)

Candidate
Yohhei Hamada
Date:
10 Aug 2024

Supervisor/ Senior Author (where appropriate)
Molebogeng X **Rangaka**
Date
16 Aug 2024

UCL Research Paper Declaration Form
referencing the doctoral candidate's own published work(s)

Please use this form to declare if parts of your thesis are already available in another format, e.g. if data, text, or figures:

- *have been uploaded to a preprint server*
- *are in submission to a peer-reviewed publication*
- *have been published in a peer-reviewed publication, e.g. journal, textbook.*

This form should be completed as many times as necessary. For instance, if you have seven thesis chapters, two of which containing material that has already been published, you would complete this form twice.

6. For a research manuscript that has already been published (if not yet published, please skip to section 2)

bb) **What is the title of the manuscript?**

A pilot cross-sectional study of non-communicable diseases in TB household contacts

cc) **Please include a link to or doi for the work**

https://www.ingentaconnect.com/contentone/iuatld/ijtldo/2024/00000001/00000004/art00002

dd) **Where was the work published?**

IJTLD OPEN

ee) **Who published the work?** (e.g. OUP)

International Union Against Tuberculosis and Lung Disease

ff) **When was the work published?**

April 2024

gg) **List the manuscript's authors in the order they appear on the publication**

Yohhei Hamada, Anicet Lugendo, Thobani Ntshiqa, Griffiths Kubeka, Julieth M. Lalashowi, Shadrack Mwastaula, Keolebogile Ntshamane, Issa Sabi, Samson Wilson, Andrew Copas, Kavindhran Velen, Nyanda Elias Ntinginya, Lilian Tina Minja, Ibrahim Abubakar, Salome Charalambous, Molebogeng X. Rangaka

hh) **Was the work peer reviewed?**

Yes.

ii) **Have you retained the copyright?**

Yes

jj) **Was an earlier form of the manuscript uploaded to a preprint server?** (e.g. medRxiv). If 'Yes', please give a link or doi)

No

If 'No', please seek permission from the relevant publisher and check the box next to the below statement:

☒

*I acknowledge permission of the publisher named under **1d** to include in this thesis portions of the publication named as included in **1c**.*

7. For a research manuscript prepared for publication but that has not yet been published (if already published, please skip to section 3)

p) **What is the current title of the manuscript?**

Click or tap here to enter text.

q) **Has the manuscript been uploaded to a preprint server?** (e.g. medRxiv; if 'Yes', please give a link or doi)

Click or tap here to enter text.

r) **Where is the work intended to be published?** (e.g. journal names)

Click or tap here to enter text.

s) **List the manuscript's authors in the intended authorship order**

Click or tap here to enter text.

t) **Stage of publication** (e.g. in submission)

8. **For multi-authored work, please give a statement of contribution covering all authors** (if single-author, please skip to section 4)

YH conceived the study and design the protocol with input from AL, LTM, IS, NEN, KV, IA, AC, SC, and MXR. YH supervised the field data collection in both sites. TN, GK, AL, JML, SM, KN, and SW coordinated the field data collection in their respective countries. YH analysed the data with advice from SC, IA, AC, and MXR. YH wrote the first draft of the manuscript, which was revised based on comments from co-authors. All authors approved the final version of the manuscript. YH had the final responsibility for the decision to submit it for publication.

9. **In which chapter(s) of your thesis can this material be found?**

Chapter 6

10. **e-Signatures confirming that the information above is accurate** (this form should be co-signed by the supervisor/ senior author unless this is not appropriate, e.g. if the paper was a single-author work)

Candidate
Yohhei Hamada
Date:
30 April 2024

Supervisor/ Senior Author (where appropriate)
Molebogeng X **Rangaka**
Date
2 May 2024

Table of Contents

List of Figures

List of Tables

1. Introduction

1.1. Global burden of tuberculosis

Annually, around 10 million people develop tuberculosis (TB), and 1.3 million die globally.[1] TB had been the leading cause of death as a single infectious agent since 2015 until the pandemic of COVID-19.[1] Almost 99% of those deaths are in low- and middle-income countries (LMIC). Eight countries, India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa, account for two-thirds of the global incident cases.[1] Morbidity and mortality caused by TB, particularly among working-age people, negatively affect economic development by causing morbidity and mortality. It is estimated that if the current trend continues, 31.8 million people will die from TB.[2] An economic loss of US$17·5 trillion globally by 2050 is predicted should this trajectory continue undisrupted.[2]

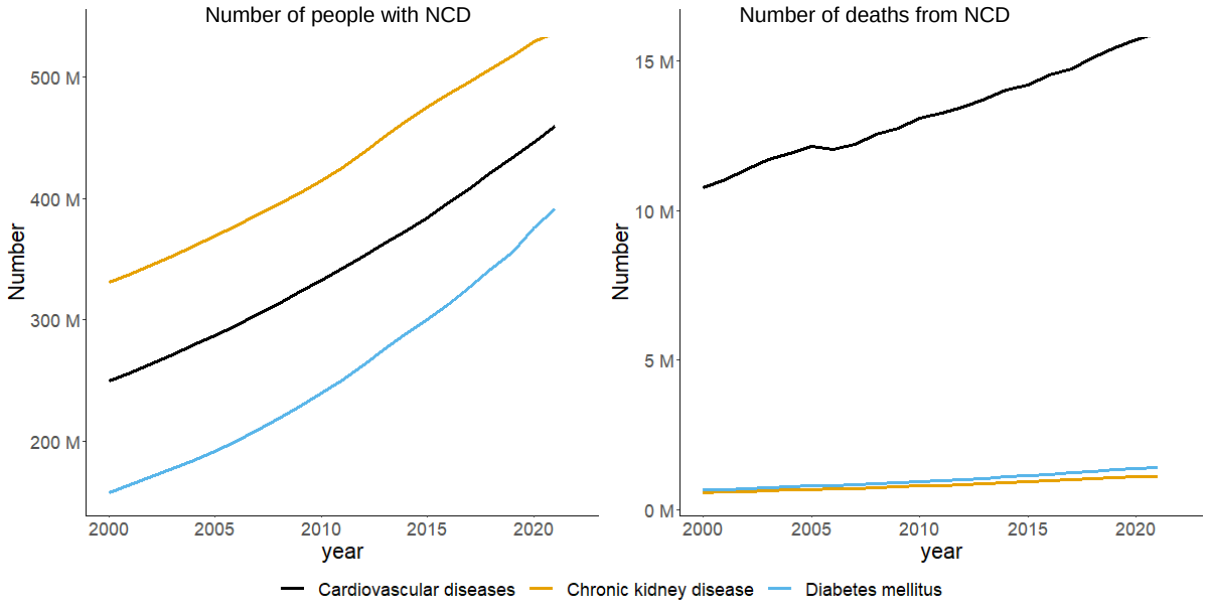
To address the global TB epidemic, the World Health Organization (WHO) defined a global strategy in 2014 called the End TB Strategy. This global strategy envisions “a world free of TB”, consisting of three strategic pillars. They include (1) integrated patient-centred care and prevention, (2) bold policy and supportive systems, and (3) intensified research and innovation.[3] The strategy defined the global targets comprising (i) the reduction of the annual TB incidence rate by 80%, (ii) the reduction of the annual number of TB deaths by 90% by 2030 compared to 2015, and (iii) ensuring that the total TB-related costs to patients with TB do not exceed 20% of their annual household income in any households by 2020.[3] The global community committed to these targets; however, the milestones for 2020 –a 35% reduction in the number of TB deaths, a 20% reduction in the TB incidence rate, and zero people with TB facing catastrophic costs - were not achieved globally. To reprioritise the End TB Strategy targets, it is essential to accelerate the implementation of comprehensive strategies outlined in the End TB Strategy. As part of Pillar One-

Integrated, Patient-Centred Care and Prevention- one essential strategy is to address non-communicable diseases (NCD) and their risk factors. WHO report in 2023 estimates that 18% of the global TB incidence is attributed to diabetes (3.7%), smoking (7.0%), and alcohol use disorder (7.4%).[1]

1.2. Burden of non-communicable diseases in low- and middle-income countries

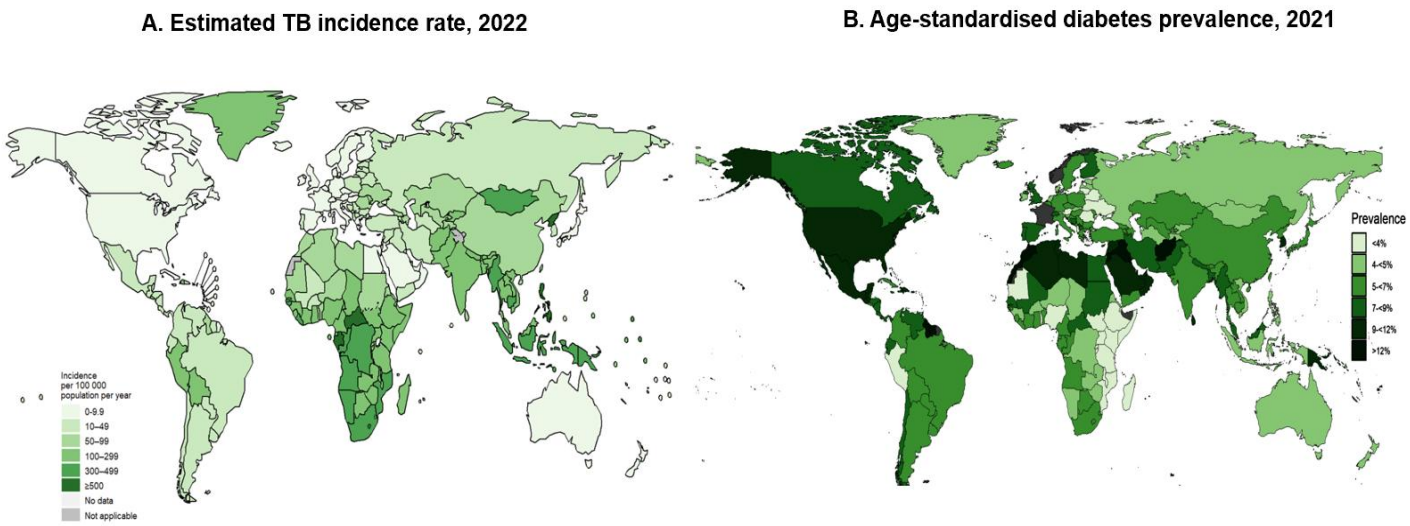
Low and middle-income countries face the rising burden of NCD, such as diabetes, cardiovascular diseases (CVDs), cancer, and chronic respiratory diseases.[4] The Global Burden of Disease estimates that, from 2010 to 2021, the number of people with NCD in LMIC increased from 5.3 billion to 6.1 billion (Figure 1).[4] Furthermore, NCD was responsible for 33 million deaths in 2021.[4] Most NCD deaths are caused by CVDs. The number of people with CVD and those dying from them, as well as those with CVD risk factors, are increasing in LMIC (Figure 1).[4] Population ageing contributed to the increase coupled with the increased prevalence of risk factors, such as unhealthy diet and smoking.[5] The substantial burden of NCD lies among working-age people aged between 30 and 69 years. With 17 million deaths per year, NCD are a leading cause of premature death and contribute an enormous economic loss.[6] A study estimated that NCD would cost US$ 500 billion per year in LMIC.[7] Recognizing the problem, one of the targets of the United Nations (UN) Sustainable Development Goal (SDG) is to reduce premature deaths from NCD by one-third by 2030.[6] However, a progress report against the SDG target published in 2020 showed that although the number of premature deaths from NCD is declining, the current speed of the decline is not sufficient to achieve the target.[8] The report called for the implementation of tobacco and alcohol control, as well as effective health system interventions such as detection and treatment of diabetes and hypertension. The rising burden of NCD in LMIC, coupled with existing high levels of TB, has led to a convergence of TB and NCD (Figre 1-2). This convergence has created a challenging syndemic that, if not addressed, could result in significant health and economic consequences for LMIC.

Figure 1-1.NCD prevalence and deaths in low and middle-income countries



Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2022.
Available from https://vizhub.healthdata.org/gbd-results/.
The plots indicate an increase in NCD in low and middle-income countries, with cardiovascular diseases as major causes of deaths.

Figure 1-2.TB incidence rate and diabetes prevalence by country



A. Reproduced from Global TB Report, World Health Organization 2023.[1] Licence: CC BY-NC-SA 3.0 IGO.
B. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2022.
Available from https://vizhub.healthdata.org/gbd-results/
These maps show a convergence of TB and diabetes, notably in Sub-Saharan Africa and Southeast Asian countries with high TB incidence rates.

1.3. Impact of NCD on TB

A landmark paper published in *The Lancet* in 2010 by a group of WHO authors advocated for addressing factors that increase the risk of developing TB. The paper highlighted diabetes as one of the drivers of TB. Diabetes and some other NCDs are known to impair immunity, either by the disease itself or its treatment, predisposing individuals to developing TB. Later, WHO guidelines on the management of TB infection in 2015 and subsequent guidelines on TB infection included people with other NCDs, such as those with end-stage renal disease requiring dialysis and people with silicosis, as at-risk populations who should be prioritized for TB preventive treatment. Certain NCDs are also noted in national guidelines on latent TB infection treatment, such as those in the UK and the US.[9,10] Furthermore, in 2022, WHO, for the first time, published a "Framework for Collaborative Action on Tuberculosis and Comorbidities," comprehensively articulating action on a range of NCDs and their risk factors.[11] In this section, I review the impact of NCDs on TB, with a particular focus on

NCD noted in WHO policy documents. Table 1-1 summarises the impact of NCD on TB.

Diabetes

Multiple systematic reviews consistently demonstrated an increased risk for TB in people with diabetes. A systematic review by Hayashi et al., including 14 studies (eight cohort and six case-control studies), reported a relative risk of 1.50 (95% Confidence interval [CI] 1.28–1.76) for developing active TB in people with diabetes than those without diabetes.[12] Another review included a greater number of papers by using a more sensitive search strategy covering studies that examined any risk factors for TB.[13] The review identified four prospective studies, and the pooled hazard ratio (HR) was 3.59 (95% CI 2.25-5.73). The exact immunological mechanism for the increased susceptibility to TB associated with diabetes remains to be understood. The current knowledge suggests that impaired innate and T-cell immunity are likely to play a role.[14]
An increased prevalence of TB infection is also reported in people with diabetes. A systematic review by Liu et al.,[15] including 20 studies, showed that people with diabetes were more likely to be infected with TB; the pooled risk ratio (RR) was 1.62 (95% CI 1.02-2.56) based on three cohort studies, and the odds ratio (OR) was 1.55 (95% CI 1.30-1.84) based on 17 cross-sectional studies. Hence, the increased TB incidence in people with diabetes may be explained by the combination of increased risk for TB infection as well as an increased risk for the development of active TB in people with TB infection. Based on the global estimate of the number of people with diabetes and the magnitude of the risk reported by Hayashi et al., WHO estimates that 0.37 million incident cases of TB were attributable to diabetes in 2022, accounting for 3.7% of total incidence cases of TB.[1]

Diabetes alters the clinical manifestation of TB and worsens its treatment outcomes. Studies have shown that people with TB and diabetes, compared to those with only TB, tend to present with pulmonary rather than extra-pulmonary TB disease.[16] Cavitary lesions are more common, associated with high bacillary

burden and smear positivity, which makes cure more difficult.[16] In a systematic review including 104 studies, people with diabetes and TB had a higher risk of death (OR 1.9, 95%CI 1.6-2.2) and relapse (OR 1.6, 95%CI 1.3-2.1) than those without diabetes.[17] Early identification and proper management of diabetes in people with TB is essential to improve the health outcomes of both TB and diabetes. In an extensive review including 200 studies globally, the pooled prevalence of diabetes among people with TB was high at 15% (95% prediction interval 2.5-36.1).[18]

Chronic kidney disease (CKD)

CKD is known to predispose individuals to TB through weakened immunity induced by various aetiologies, such as oxidative stress and inflammation, vitamin D deficiency, and malnutrition.[19] The risk is highest in people with end-stage renal disease (ESRD). A systematic review including 12 studies found that when pooling adjusted incidence rate ratios from three studies, there was a 3.6 times higher risk of TB in people with ESRD than in the general population.[20] Accordingly, people receiving dialysis are one of the at-risk populations for whom WHO strongly recommends systematic testing and treatment of TB infection.[21] Moreover, the risk appears elevated in people with CKD who are not on dialysis. In a recent systematic review including five studies, the risk of TB was 57% higher in people with CKD stages 3-5 than those without CKD (HR 1.57, 95% CI 1.22-2.03).[22]

Because of the impaired cellular immunity, people on dialysis and those who received renal transplantation tend to present with extrapulmonary TB.[19] The presence of CKD complicates the treatment of TB because of the need for dose adjustment of anti-TB drugs or other medications used to treat common complications such as hypertension. Among commonly used anti-TB drugs, ethambutol, pyrazinamide, and levofloxacin are renally excreted and thus require dose adjustment.[19]

Cancer

People with cancer are at an increased risk for TB because of immunosuppression induced by the cancer itself and their treatment. A stronger link has been documented for haematologic malignancies, specific types of solid cancer (e.g. neck, head, and lung), and individuals who had gastrectomy or jejunoileal bypass.[23,24] Accordingly, the US Centers for Disease Control and Prevention (CDC) has recommended treatment of TB infection for people with those conditions.[9] The UK NICE guidelines note an increased TB risk in slightly different groups: people with a haematological malignancy, those having chemotherapy, and those who have had gastrectomy or jejunoileal bypass.[10] A systematic review by Cheng et al. reported an increase in TB risk associated with various types of cancer, including haematologic, lung, head and neck, and other cancers.[23] However, the review calculated incident rate ratios using WHO TB incidence estimates as references instead of directly comparing TB incidence within studies. A later review addressed this limitation by including studies with a control group.[24] The review included 13 studies overall comprising 921,464 patients with cancer. The incident rate ratio (IRR) was 2.25 (95% CI 1.96-2.58) in patients with solid cancer and 3.53 (95% CI 1.63-7.64) in those with haematological cancers.

There is limited data on TB treatment outcomes in people receiving anti-cancer therapy, but small studies reported the safety and effectiveness of concurrent treatment of cancer and TB. [25,26]

Chronic respiratory diseases

Pneumoconiosis, such as silicosis, is a strong risk factor for TB.[21] In a recent review,[27] people with silicosis had a 4-fold higher risk for TB than those without it (RR 4.01, 95% CI: 2.88, 5.58, 8 studies). Recognising a paucity of data on the risk of TB in people with other respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, I conducted a systematic review to investigate the risk of TB in association with these respiratory conditions.[28] My review showed that people with COPD are at a 1.4-3.1 higher risk of incident TB.[28] However, a causal association between COPD and the development of

active TB is unclear. Impaired cellular immunity and macrophage function in people with COPD might explain the increased risk of TB.[29] However, there are other underlying factors that might explain the association between COPD and TB, such as smoking and socioeconomic status. The presence of COPD is reported to be associated with a higher risk of death and hospitalization from TB.[30,31] Thus, prevention of TB is essential in people with COPD. However, current WHO guidelines do not recommend systematic testing and treatment of TB infection in this group.[21]

Mental health conditions

Studies report a high prevalence of depression among people with TB. In a systematic review and meta-analysis including 25 studies from seven countries, nearly half of people with TB had depression (a pooled prevalence of 45.2%, 95% CI 38.0-52.6).[32] The prevalence was higher in people with multidrug-resistant (MDR)-TB (52.3%, 95% CI 38.1-66.2) than people with non-MDR TB, although the prevalence among the latter group remained high at 43.5% (95% CI 35.9-51.4). A combination of psychosocial, socioeconomic, and physiological factors may explain the overlap of TB and depression. The stigma associated with TB can lead to social isolation and reduced quality of life, contributing to depressive symptoms.[33] In addition, the financial burden, prolonged treatment, and side effects of medications can exacerbate stress and predispose individuals to depression.[34] Conversely, the risk of TB may be increased in people with mental health conditions such as depression and schizophrenia. A systematic review published in 2020 identified two cohort studies in Taiwan and South Korea, both of which showed a higher TB incidence in people with depression than those without it (HR 1.15, 95% CI 1.03-1.28 and 2.63, 95% CI 1.74-3.96, respectively).[35] The increased risk may be a result of shared risk factors such as alcohol use and poverty.[35] In addition, impaired immunity associated with depression might increase the risk of TB development.[35]

The presence of mental health conditions can negatively affect TB treatment outcomes.[36] A systematic review in 2020 included nine studies evaluating TB treatment outcomes in meta-analysis.[36] While the point estimates were consistent with a poor outcome in people with mental health conditions (OR 2.13, 95% CI: 0.85-5.37 for any poor outcome, OR 1.90, 95% CI 0.33-10.91 for loss to follow up, and OR 1.60, 95% CI 0.81-3.02 for non-adherence), the estimates were imprecise due to the small number of studies and heterogeneity.

Table 1-1.Summary of the impact of NCD on TB

NCD	Impact on TB risk	Impact on clinical manifestation/treatment outcome	References
Diabetes	• 1.5-3.5-fold increase in the risk of developing TB • 1.6-fold increase in the prevalence of TB infection	• More likely to present with pulmonary TB and with cavitary lesions. • Higher risk of death and relapse	13,14,16,17,18
Chronic kidney disease	• 3.6-fold increase in the risk of developing TB in people with ESRD • 1.6-fold increase in developing TB people with CKD stages 3-5	• Complicates TB treatment due to the need for dose adjustment of anti-TB drugs (e.g. ethambutol, pyrazinamide, and levofloxacin)	20,21,23
Cancer	• Increased risk for TB, especially in haematologic malignancies (3.5-fold) and specific solid cancers, such as neck, head, and lung (2.2-fold)	• Limited data on TB treatment outcomes in people with cancer	24, 25
Chronic respiratory diseases	• 4-fold increase in the risk of developing TB in people with silicosis • 1.4-3.1-fold increased risk of developing TB in people with COPD	• A study reported a 2-fold increased risk of death from all causes within the first year after TB diagnosis than the general population.	28,29,31,32
Mental health conditions	• Higher TB incidence in people with depression (HR 1.15 and 2.63 in two studies)	• A review reported poorer TB treatment outcomes with a wide confidence interval without a statistical significance (OR 2.13, 95% CI: 0.85-5.37 for poor outcomes). • High prevalence of depression among people with TB: 45.2% (95% CI 38.0-52.6).	33,36,37

TB: Tuberculosis; ESRD: End-Stage Renal Disease; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; HR: Hazard Ratio; OR: Odds Ratio; CI: Confidence Interval

1.4. Impact of TB on NCD

Both acute and chronic infections have been linked to the development and worsening of NCD. Chronic inflammation induced by chronic infectious diseases, such as HIV, has been associated with an increased risk of cardiovascular diseases.[37] It is also well known that acute infections, such as SARS-CoV-2, exacerbate glycemic control through acute inflammation and increased insulin resistance.[38] TB is not an exception. This section summarises the impact of TB on NCD (see Table 1-2 for a summary).

Diabetes

TB is known to induce hyperglycaemia through TB-related systemic inflammation.[39] While blood glucose levels return to normal after TB treatment, hyperglycemia persists in some patients.[39] In a recent systematic review, almost a quarter of TB patients had newly detected hyperglycaemia at baseline, and half did not resolve at the end of follow-up; however, the proportion of those hyperglycaemia that resolved was heterogeneous across studies.[40]
It remains unclear whether TB increases the risk of developing diabetes, not only a transient increase in blood glucose levels. A study using UK primary care data suggested it might be possible.[41] The risk for diabetes was significantly higher in individuals with a history of TB disease (IRR 5.65, 95% CI 5.19-6.16) than those without, after adjusting for age, sex, region, degree of deprivation, and smoking status. Furthermore, a study in the US reported an increased incidence of diabetes in people with TB infection than those without it (HR 1.2, 95% CI 1.2-1.3).[42] It is unknown if the treatment of TB infection can lower the risk of diabetes.

Cardiovascular diseases

A small number of studies suggest that TB may increase the risk of CVD. A systematic review published in 2020 found four cohort studies, and the pooled RR for CVD was 1.76 (95% CI, 1.05–2.95) in people with TB compared to those without TB.[43] It is hypothesised that systematic inflammation induced by TB

promotes the development of atherosclerotic plaque and its rupture.[39] Of note, a similar link has been observed in other infectious agents, such as HIV and Chlamydia pneumoniae.[39] It is, therefore, not surprising that TB is associated with the development of cardiovascular diseases. Interestingly, another review reported an increased risk of coronary artery disease in people with TB infection (OR 2.15, 95% CI 1.48- 3.12).[44] However, the review included only two case control and two cross-sectional studies, and cohort studies were lacking. Thus, the association needs further confirmation by cohort studies.

Chronic respiratory diseases

TB can cause long-term lung sequalae, also known as post-TB lung disease.[45] Post-TB lung disease has diverse clinical manifestations, such as airway obstruction and bronchiectasis. Host immune response to TB likely drives lung remodelling, resulting in lung function impairment.[45] A meta-analysis including 21 cross-sectional studies reported an increased prevalence of COPD in people with prior history of TB than those without (OR 2.59; 95% CI: 2.12–3.15).[46] The finding was consistent when adjusting for multiple covariates, including smoking. Similarly, another review found that 17.8% of people who were treated for TB had airway obstruction based on spirometry compared to 5.4% in control groups.[47] In LMIC with a high level of TB incidence, TB plays an important role in the development of chronic respiratory disease. A nationwide study in Uganda estimated that 6% of chronic respiratory symptoms were attributed to a history of TB, a level similar to smoking (7%).[48]

Cancer

Studies have reported an association between TB and subsequent development of lung cancer. In a recent systematic review, previous TB was significantly associated with the later diagnosis of lung cancer both in cohort studies (HR 1.77, 95%CI 1.41-2.22) and case-control studies (OR 1.76, 95% CI 1.41-2.19), when pooling estimates that were adjusted at least for age and smoking history.[49] The risk remained similar when adjusted for smoking history

quantitatively. These findings suggest that smoking history alone, which increases the risk for both TB and lung cancer, cannot explain the association. It is hypothesised that chronic inflammation in the lung caused by TB promotes the development of lung cancer.[49] It is, however, challenging to exclude the influence of other factors.[49] First, residual confounding may be possible due to shared risk factors such as environmental exposure to air pollution. Second, lung cancer, which was not detected at the time of TB diagnosis, might have increased the risk of TB (i.e. reverse causation). Third, people with TB might have had more chances of having lung cancer diagnosed due to an increased frequency of chest X-rays.

Table 1-2.Summary of the impact of TB on NCD

NCD	Impact of TB on NCD	References
Diabetes	• Transient hyperglycemia, but some cases are persistent. • Unclear if TB increases the risk of developing diabetes. One study in the UK reported a higher risk for diabetes associated with a history of TB (IRR 5.65, 95% CI 5.19-6.16).	40,41,42
Cardiovascular diseases	• Increased risk of CVD in people with TB (pooled RR 1.76, 95% CI 1.05–2.95, 4 cohort studies). • Higher risk of coronary artery disease (OR 2.15, 95% CI 1.48-3.12, 2 case-control and 2 cross-sectional studies).	44.45
Chronic respiratory diseases	• Post-TB lung disease, including airway obstruction and bronchiectasis, driven by host immune response to TB. • Increased prevalence of COPD in people with a history of TB (OR 2.59, 95% CI 2.12–3.15). • Airway obstruction post-TB (17.8% of people treated for TB compared to 5.4% in control groups in a review).	46,47,48
Cancer	• Increased risk for lung cancer in people with previous TB (HR 1.77, 95% CI 1.41-2.22 in cohort studies; OR 1.76, 95% CI 1.41-2.19 in case-control studies). • Chronic lung inflammation caused by TB may promote lung cancer development, but other explanations are possible (see text)	50

TB: Tuberculosis; IRR: Incidence Rate Ratio; CI: Confidence Interval; CVD: Cardiovascular Disease; RR: Relative Risk; OR: Odds Ratio; COPD: Chronic Obstructive Pulmonary Disease; HR: Hazard Ratio

1.5. Shared risk factors for TB and NCD

There are shared risk factors for both TB and NCD. These include key health-related determinants of TB, covered under SDG3 and highlighted in the global TB report, such as smoking, undernourishment, alcohol use disorders, and HIV.[1] Additionally, there are broader social determinants of TB, addressed in other areas of the SDGs, including poverty and indoor air pollution. These shared risk factors promote the convergence of TB and NCDs at both individual and population levels. Conversely, addressing these shared risk factors can significantly reduce the adverse impact of both conditions. Here, I summarise the key shared risk factors for TB and NCDs in line with those highlighted in the WHO global TB report (see Table 1-3 for a summary).

Smoking

Smoking is a well-established risk factor for TB and various NCD. Smoking affects innate and adaptive immunity to control TB, such as impairment of mucus and mucociliary clearance, alveolar macrophages, and T-cell response.[50] Multiple systematic reviews demonstrated an increased risk for TB infection, TB disease, and poor TB treatment outcomes associated with smoking.[51-53] In one of those systematic reviews, the risk ratio was 1.73 (95% CI, 1.46-2.04) for TB infection and 2.27 (95%CI, 1.90-2.71) for TB disease in smokers than non-smokers.[51] Another review found that smoking was associated with approximately a 2-fold increased risk of recurrence.[54] The association was observed not only in current smokers but also in former smokers. The same review reported that people with active TB who are current or ever smokers are more likely to die during TB treatment than non-smokers (RR 1.51; 95% CI, 1.09-2.10 for current smokers).[54]

It is also likely that second-hand smoking is associated with an increased risk for TB. A systematic review reported a 2-fold higher risk for active TB in adults who were exposed to smoking and > 3-fold in children.[55] The associations remained significant after adjustment of age, socioeconomic status, and

household contact with a person with TB. In contrast, the association between second-hand smoking and TB infections is less clear. In the same review, while a meta-analysis including all studies found an increased risk for TB infection in adults and children, the association was not significant in a sub-group of studies that adjusted for socioeconomic status.[55] Another review reported a similar finding, a significant association of second-hand smoking with active TB but not with TB infection.[56]

For NCD, smoking is one of the major risk factors, demonstrated by the numerous body of evidence. One in six deaths caused by NCD globally is attributed to smoking.[57] Smoking is associated with a range of NCDs, including cancer, cardiovascular diseases, COPD, CKD, and diabetes. In 2022, Nature Medicine published a burden-of-proof study that synthesised the effects of smoking on various health outcomes.[58] The magnitude of the association was strongest for lung cancer, laryngeal cancer, aortic aneurysm, and peripheral artery disease, associated with >100% increase in risk, on average. Greater smoking consumption was associated with an even higher risk for these diseases. The global prevalence of smoking has decreased by 37.7% in females and by 27.5% in males since 2019.[59] However, because of population growth, the absolute number of people who smoke is increasing. The latest data indicates that there are 1.3 billion current smokers, and around 80% of them are in LMIC.

Household and ambient air pollution

Polluting fuels and technologies are still commonly used for cooking and heating in LMIC.[60] These include open fires and inefficient stoves fuelled by kerosene, biomass, and coal. WHO estimates that around a third of the global population uses these fuels for cooking.[60] Household air pollution is linked to various adverse effects, including TB and NCD. In a recent systematic review, household air pollution was associated with an increased risk of TB (RR 1.26, 1.08−1.48), based on a meta-analysis of 53 studies.[61] The same review reported an association with COPD (RR 1.70, 95% CI 1.47-1.97), lung cancer

(RR 1.69, 95% CI 1.44-1.98), and cardiovascular diseases (RR 1.09, 95%CI 1.04-1.14 for cerebrovascular disease and RR 1.10, 95%CI 1.09−1.11 for ischemic heart disease).[61]

Ambient air pollution has similar adverse health effects. Studies have shown an increased incidence of TB associated with an increase in air concentration of PM2.5 (RR 1.12, 95% CI 1.06–1.19), PM10 (RR 1.06, 95% CI 1.01–1.12), and SO2 (RR 1.08, 95% CI: 1.04–1.12).[62] Likewise, ambient air pollution increases the risk of lung cancer, chronic respiratory diseases, and cardiovascular disease, among others.[63] In 2019, WHO estimated that ambient air pollution caused 4.2 million premature deaths, and it was considered that 37% and 18% of them were due to CVD and COPD, respectively.[64]

HIV

TB is the leading cause of hospitalization and death in people living with HIV. The latest WHO data suggests that people living with HIV are at 16 times higher risk of incident TB than people without HIV.[65] The risk is highest in people with a low CD4 count, but the TB risk is elevated soon after HIV infection, even at a high CD4 count.[66] Hence, other pathways than depletion of CD4 count, including the functional impairment of Mycobacterium tuberculosis (MTB)-specific T cells and the impaired innate immunity, contribute to this increased TB risk in the early stages of HIV infection.[66]

In addition to TB, people living with HIV are at an increased risk for NCDs, such as CVD and cancer. Contributing factors include not only common risk factors like smoking but also HIV-specific factors. These include chronic inflammation triggered by HIV and other pathogens promoted by CD4 depletion, as well as some antivirals.[67] A systematic review highlighted that people living with HIV had a greater risk of myocardial infarction compared with those without HIV (RR 1.73, 95% CI 1.44-2.08).[68]

People with HIV are at substantially higher risk of AIDS-defining cancers such as Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer, which are

linked to infection by other viruses such as Human Herpesvirus 8, Epstein-Barr Virus, and Human Papillomavirus. People with HIV are also at an increased risk for non-AIDS-defining cancers not linked to other viral infections. In a large nationwide study in the US, people with HIV had a 2-fold higher risk of lung cancer than the general population.[69] In addition, people with HIV are likely at a greater risk for other NCDs, including diabetes, hypertension, and kidney disease.[70-72] Depression is common in people with HIV. In a review, the pooled prevalence of depression was 30% among people living with HIV in Sub-Saharan Africa.[73]

Alcohol

The harmful use of alcohol, drinking that causes detrimental health and social consequences for the drinker,[74] is one of the risk factors for TB that are monitored by WHO under the WHO TB-SDG monitoring framework.[1] In a systematic review published earlier in 2007, a high alcohol consumption of over 40 g alcohol per day or an alcohol use disorder was associated with over 3-fold higher risk for TB (RR 3.50, 95% CI 2.01-5.93) than a lower level of alcohol use.[75] Later reviews additionally reported an increased risk for TB associated with any alcohol use.[76,77] In one review, any alcohol use was associated with a significantly elevated risk for TB (RR 1.35, 95% CI 1.09-1.68), even though the magnitude of the risk was lower than that for the harmful use of alcohol (RR 3.33, 95% CI 2.14-5.19).[77] Another review showed similar results, in which any alcohol use was associated with TB with an OR of 1.60 (95%CI 1.39-1.84).[76] Two causal pathways are proposed.[77] First, like smoking, alcohol use can impair both innate and adaptive immunity through the direct effects of alcohol as well as complications caused by alcohol, such as liver disease and malnutrition. Second, people who drink alcohol may be more likely to spend time in environments with high TB transmission, such as bars and prisons.

Alcohol use is also associated with poor TB treatment outcomes. In a review including 111 studies, alcohol use was associated with 2-fold higher odds of poor treatment outcomes, including death, treatment failure, and loss to follow-

up), both in people with drug-susceptible and drug-resistant TB.[78] Another review reported a higher risk of relapse (OR 3.64, 95% CI 2.26-5.88) in people with TB drinking alcohol.[79]

Alcohol use is associated with a wide range of NCD, including various types of cancer, cardiovascular diseases, diabetes, digestive diseases, and liver cirrhosis.[80] In an estimate published in 2020, 1.7 million NCD deaths were attributed to alcohol in 2016, corresponding to 65.4 million disability-adjusted life years.[80]

Malnutrition

Malnutrition encompasses both insufficient and excess intake of nutrients.[81] The former condition is referred to as undernutrition, which is associated with an increased risk for TB.[82] Undernutrition is estimated to account for around 20% of all cases of incident TB globally[1], representing the largest proportion among risk factors identified by WHO.

Studies have shown an inverse relationship between body weight and TB incidence. A review in 2010 found a reduction in TB incidence of 13.8% (95% CI 13.4−14.2) per unit increase in body mass index (BMI).[83] A recent large nationwide cohort study in the Republic of Korea also reported that underweight was associated with a 2-fold increase in the risk for TB incidence compared with normal weight.[84]

Underweight is common among people with TB because of its bidirectional association with TB; TB can cause wasting,[85] whereas underweight is a risk factor for TB. In a recent systematic review, the prevalence of underweight in people with TB was three times higher than in people without TB.[86] Furthermore, being underweight may worsen TB treatment outcomes. In a systematic review of people with MDR-TB, underweight was associated with an increased risk of death (OR 2.8, 95% CI 2.1-3.6) and unsuccessful treatment outcomes (OR 1.8, 95% CI 1.5-2.1).[87] Conversely, obesity is associated with a lower risk for TB. A review reported a significant decline in the risk for TB in

people with obesity compared to those with normal weight (OR 0.26, 95% CI 0.24-0.27).[86] This is of interest given that there is a clear association between obesity and diabetes, while diabetes increases the risk for TB. A study in Taiwan demonstrated, through causal mediation analysis, that while a higher BMI indirectly increased TB risk because of its linkage with diabetes, the overall association remained protective, driven by its direct protective effect.[88] However, the biological mechanisms for the protective effect of obesity remain to be understood. One proposed hypothesis is a high leptin level, which promotes proliferation and activation of T-cell lymphocytes.[86]

For NCD, overweight/obesity is one of the key metabolic risk factors. It is associated with various types of NCD, including cardiovascular diseases, diabetes, hypertension, and asthma.[89,90] In addition, obesity is found to be a risk factor for several cancers, such as breast, kidney, and colon cancers.[91] Because of its association with multiple diseases, people with obesity tend to have multiple diseases (i.e. multimorbidity). One recent study showed that individuals with obesity were over ten times more likely to have four or more obesity-related diseases than those with normal weight.[90] Furthermore, using data from the global burden of disease study 2019, Chong et al. estimated that 5 million deaths worldwide were attributed to obesity in 2019.[92]

Poverty

Poverty is an important determinant of TB. People in poverty are exposed to multiple risk factors, such as poor living and working conditions marked by crowding and poor ventilation, indoor air pollution, and malnutrition.[82] Smoking is more common in people from lower socioeconomic status.[93] The association between socioeconomic status and alcohol use has shown mixed results and is likely to vary by region and country.[94,95] Studies in Southeast Asia tended to show that alcohol use was more common in individuals of lower socioeconomic status.[94] In contrast, early studies in Africa showed the opposite (i.e. a higher alcohol consumption in individuals of higher socioeconomic status).[94] Poor access to health care among people in poverty may delay TB diagnosis and

promote TB transmission in their community. An ecological analysis using national data indicated that countries with higher spending on social protection were associated with lower TB incidence, prevalence, and mortality.[96]

Recognizing the critical need to address social determinants of TB, WHO monitors access to clean fuels, income inequality, poverty, social protection and housing conditions as part of a framework for monitoring the SDG related to TB.[1]

There is clear evidence that NCD, in general, are more common in individuals with low economic status than those with high economic status in high-income countries.[97] In contrast, the association is more complex in LMIC. As aforementioned, smoking is more common in people with lower economic status, while the use of alcohol in people with low socioeconomic status varies by setting. On the other hand, people from high economic status have more access to salty and high-fat foods and engage in less physical activities than those from low economic status.[95] A recent systematic review examined diabetes prevalence by education status and wealth in LMIC.[98] The review found that a higher education level was associated with a higher prevalence of diabetes (RR 1.36, 95% CI 1.22-1.52) after adjustment for age, sex, and wealth. Similarly, people with the highest wealth quintile were more likely to have diabetes (RR 1.19, 95% CI 1.03-1.36) than those with the lowest wealth quintile.

For hypertension, a systematic review of national surveys in 76 LMIC did not find a clear association between hypertension prevalence and household wealth quintile or educational attainment. There was an exception in Southeast Asia, where hypertension was significantly more common in people with greater wealth (RR for wealthiest vs least wealthy quintile: 1.28, 95% CI 1.22-1.34).[99]

Although the prevalence of NCDs may not necessarily be higher in people of low socioeconomic status than those of high socioeconomic status, they may experience poorer access to health care, leading to a higher likelihood of inadequate NCD treatment. A cross-sectional survey conducted in clinics of 12

Sub-Saharan countries reported that hypertension was less likely to be controlled in individuals of lower socioeconomic status. In people from low, middle, and high socioeconomic status, the proportion of uncontrolled hypertension was 81.8%, 79.3%, and 72.8%, respectively.[100]

Table 1-3.Summary of shared risk factors for TB and NCD

Risk factors	Association with TB	Association with NCD	References
Smoking	• Increased risk for TB infection, disease, and poor TB treatment outcomes. E.g., a 2.2-fold increase in the risk of developing TB disease. • Second-hand smoking associated with an increased risk for TB disease (2-fold in adults).	• Smoking is a major risk factor for various NCDs, such as cancer, cardiovascular diseases, COPD, CKD, and diabetes, responsible for 1 in 6 NCD deaths globally.	52,55,56,58
Air Pollution	• Household air pollution associated with a 1.3-fold increased risk for TB disease. • Ambient air pollution also associated with an increased incidence of TB.	• Household air pollution associated with respiratory diseases (e.g., COPD), lung cancer, and cardiovascular diseases. • Ambient air pollution associated with various NCD including lung cancer, chronic respiratory diseases, and cardiovascular disease.	62,63,64
HIV	• Well-established risk factor for TB, with a 16 times higher risk of incident TB. • Increased risk with low CD4 counts.	• Associated with an increased risk for various NCD, including cardiovascular disease, diabetes, kidney disease, depression, and cancer (both AIDS-defining and non-AIDS-defining cancers).	66,67,68,70,71,72,73,74
Alcohol	• High alcohol consumption (> 40 g/day) or alcohol use disorder associated with a 3.5-fold increase in TB risk, with a smaller risk associated with any alcohol use (1.4-fold). • Also associated with poor TB treatment outcomes.	• One of the major risk factors for NCD, responsible for 1.7 million NCD deaths per year. • Associated with various NCDs, including cancer, cardiovascular diseases, and liver cirrhosis.	76,77,78,79,81
Malnutrition	• Undernutrition is linked to higher TB incidence and worse outcomes, whereas higher BMI is linked to a lower TB incidence.	• Overweight/obesity is a key metabolic risk factor associated with various NCD. • Around 5 million deaths worldwide, attributed to obesity annually.	83,84,88,87,90,91
Poverty	• Poverty is a determinant of TB, linked to multiple risk factors such as poor living conditions, air pollution, malnutrition, and limited access to healthcare.	• NCD are more common in individuals with low economic status in HIC, while the association varies in LMIC. • Poorer access to healthcare leads to inadequate NCD treatment.	83,98,99,100,101

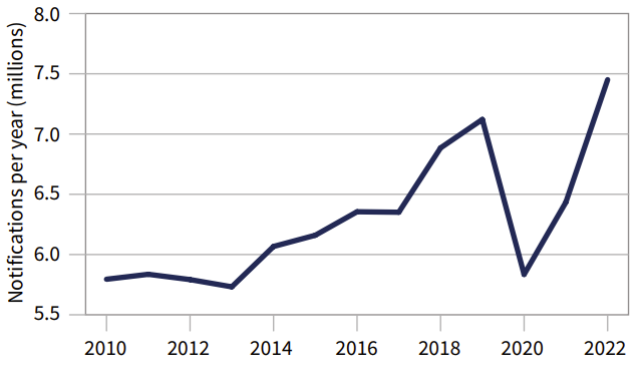
TB: tuberculosis: NCD: non-communicable disease; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; LMIC: low- and middle-income countries; HIV: high-income countries

1.6. The impact of COVID-19 on TB and NCD

The COVID-19 pandemic, caused by SARS-CoV-2, highlighted the importance of addressing ongoing epidemics of TB and NCDs. Failure to address them leaves us vulnerable to existing and emerging diseases, as demonstrated by the disruption of TB and NCD services by COVID-19 and the increased risk of severe disease and deaths in those with underlying conditions. Furthermore, COVID-19 remains a major threat with the emergence of new variants, even though the number of new cases and deaths has declined.[101] This section, therefore, summarises the impact of COVID-19 on TB and NCD.

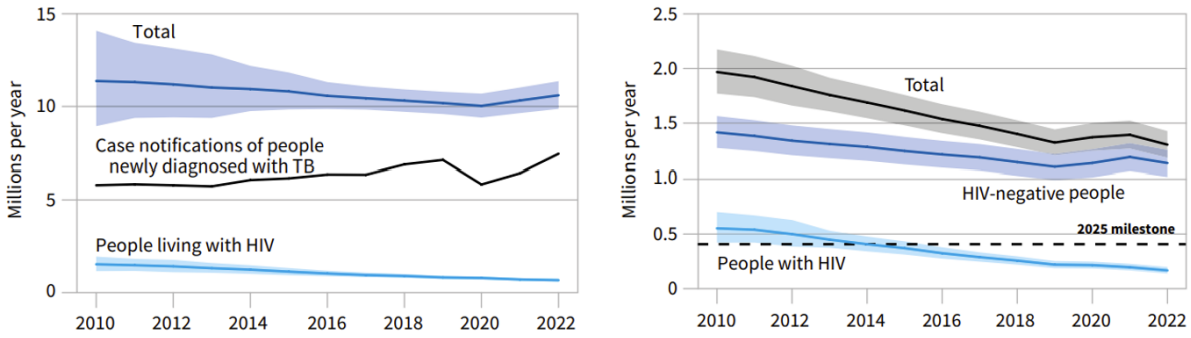
The pandemic of COVID-19 has killed 7.0 million people globally as of November 2023.[102] The pandemic disrupted essential health services, including those for TB. As a result, the number of TB cases notified declined significantly (from 7.1 million to 5.8 million between 2019 and 2020), followed by a recovery in 2022 (7.5 million) (Figure 1-3).[1] The negative impact of COVID-19 led to an increase in the number of incident TB cases and deaths increased (from 1.2 million to 1.3 million) (Figure 1-4).[1] Similarly, COVID-19 has affected NCD services. In a global survey by WHO, 136 countries reported the disruption of NCD services.[103] Its impact may extend for years unless addressed urgently.

Figure 1-3.Global trend in case notifications of people with TB



Reproduced from Global TB Report, World Health Organization 2023.[1] Licence: CC BY-NC-SA 3.0 IGO.
The plot shows the impact of health service disruptions due to COVID-19 on TB case notifications; case notifications declined in 2020, followed by a recovery in 2022.

Figure 1-4.Global trend in estimated number of incident TB cases (left) and deaths (right)



Reproduced from Global TB Report, World Health Organization 2023.[1] Licence: CC BY-NC-SA 3.0 IGO.

The plots show the impact of health service disruptions due to COVID-19 on the burden of TB; TB incidence and deaths rebounded following the pandemic.

The biological impact of COVID-19 on TB is less well understood. Immunological studies have suggested that SARS-CoV-2 infection may increase the risk of TB reactivation through T cell depletion and inflammatory responses in the lung.[104] However, epidemiological evidence on the increased TB risk is limited. One study published in 2023 explored this association using data on regional insurance claims in Thailand.[105] The study found that individuals who were diagnosed with COVID-19 pneumonia had a higher incidence of TB within 0–30 days after the diagnosis of COVID-19 (HR 9.87, 95% CI 5.64-17.30) as well as in a later period between 31–300 days (HR 7.15, 95% CI 5.54-9.22) compared to the general population that had never been tested for COVID-19.

It is now well-recognised that people with NCD are susceptible to COVID-19 and experience a high mortality rate.[106] For example, diabetes is associated with a 3-fold higher risk of death due to COVID-19.[107] Conversely, COVID-19 can exacerbate pre-existing NCD but also increase the risk for developing new NCDs through indirect and direct effects.[108] Indirect effects include inactivity due to social isolation, psychological stress, substance use, and disruption of health services.[108] In addition, COVID-19 induces vascular, myocardial, and pancreatic injury. A study using the national veteran's databases in the US reported an

increased incidence of a range of cardiovascular diseases, such as stroke, ischemic heart diseases, and dysrhythmia, post-COVID-19.[109] A systematic review found that COVID-19 was associated with a higher risk of new-onset diabetes (RR, 1.66, 95% CI 1.38-2.00), based on eight retrospective cohort studies.[110] Addressing the ongoing dual epidemic of TB and NCD and reducing their burden is critical to mitigating the impact of COVID-19 and strengthening resilience against existing and new infectious diseases.

1.7. Screening of TB and NCD

According to WHO, screening "identifies people in an apparently healthy population who are at higher risk of a health problem or a condition, by means of tests, examinations or other procedures, so that an early treatment or intervention can be offered".[111] In general, screening programmes aim to reduce morbidity and mortality through early detection and early treatment of a condition. In the case of communicable diseases, the aim can also include preventing transmission to others. This section reviews the rationale, evidence, and international recommendations for screening TB and NCDs, respectively.

Systematic screening and household contact investigation for TB

Under-detection of people with TB disease has been an obstacle to achieving the End TB targets, further compounded by the pandemic of COVID-19.[1] One of the strategies that can help find more people with TB and place them on treatment is systematic screening. WHO defines systematic screening as "the systematic identification of people at risk for TB disease, in a predetermined target group, by assessing using tests, examinations or other procedures that can be applied rapidly."[112] In routine care, TB investigations are normally initiated when patients seek care in clinics because of TB symptoms, which is often referred to as "passive case finding". In contrast, systematic screening is usually provider-initiated and applies TB investigations to pre-defined groups according to a set of screening procedures. Individuals who meet pre-defined screening criteria receive confirmatory testing for TB. One of the priority groups for systematic screening is household and other close contacts of individuals

with TB disease.[112] The prevalence of TB disease is high among household and close contacts. A systematic review that informed the WHO guidelines found a pooled TB prevalence of 3.6% (95% CI 3.3-4.0).[112] Furthermore, a cluster RCT in Viet Nam showed an increase in TB notification by implementing household contact tracing compared to a passive case finding alone (RR 2.5, 95% CI 2.0-3.2).[113]

Recognizing the vital role of contact investigation to End TB, the coverage of contact investigation is one of the top 10 indicators for monitoring implementation of the End TB strategy, with a target of > 90% by 2025.[114] The coverage of contact investigation has been increasing globally. In 2022, the coverage among contacts of bacteriologically confirmed pulmonary TB has risen from 55% in 2020 to 80%, out of 8.9 million contacts reported globally.[1] However, there are gaps in the data. First, data from 40% of the WHO member states is not available. Second, the data might miss the number of household contacts that were not identified or reported. For example, Nigeria reported 366,537 contacts, of whom 94% were evaluated for TB. However, the number of contacts is small considering that Nigeria notified 222,279 bacteriologically confirmed TB in the same year, and the national average household size is around five persons.[115] Third, the proportion of index TB cases whose household contacts have been evaluated is unknown. A study in Uganda reported that among 338 index people with TB, home visits were scheduled only for 61% of them.[116] Such an initial loss is not being measured with the current monitoring framework, which starts with the number of contacts identified.

There are multiple challenges in implementing contact investigation. They include knowledge gaps among both health care providers and clients, perceived low risk for TB, stigma, and access to care such as costs for transportation and investigations as well as time for travel and waiting in clinics.[117] Recently, a cluster randomised controlled trial (RCT) in Cameroon and Uganda evaluated a “community-based approach” in which screening is

delivered by community workers at home compared to a “facility-based approach” in which index TB patients were asked to bring their household members to health care facilities.[118] The community-based approach substantially increased screening coverage among contacts (81.9% vs 47.3%).[118] However, conducting home visits may be more resource-intensive and might not be feasible in settings with limited human resources and budgets.

Screening for NCD in low and middle-countries

Like TB, there is a large gap in the diagnosis of NCD in LMIC. Globally, around one-third of adults aged 30–79 years have hypertension, yet only 54% of them are aware of having it, and 42% of those with hypertension are on treatment.[119] The gap is more prominent in low-income countries, where only 26% of adults with hypertension are on treatment compared to 58% in high-income countries.[119] Because of the asymptomatic nature of hypertension, screening is essential to find and treat people with hypertension early and prevent its complications. The International Society of Hypertension launched an annual global campaign in 2017 to raise awareness of blood pressure measurement, named May Measurement Month.[120] In 2019, 92 countries participated in the campaign, and 1.5 million people were screened for hypertension. For a third of them, it was their first blood pressure measurement. [120] Blood pressure measurement is particularly important in adults with CVD risk factors. WHO PEN guidelines highlight the importance of blood pressure measurement in adults with the following risk factors: history of CVD, diabetes, CKD, smoking, obesity, and family history of CVD.[121] It is of note, however, that the WHO recommends routine blood pressure measurement in adults during their primary care visit as the priority route to find people with hypertension rather than population-based screening.[119] This is because of the potential challenge in linking people who are found to have hypertension through population-based screening to care and effective follow-up.

There is also a large gap in the detection of diabetes. An individual data meta-analysis of nationally representative surveys in 55 LMIC found a pooled

diabetes prevalence of 9.0% (95% CI 8.7-9.4). Over half of them were not aware of their diabetes prior to the surveys.[122] Similar to hypertension, diabetes is often asymptomatic at an early stage. Accordingly, the WHO PEN guidelines recommend testing for diabetes in adults who are symptomatic but also in asymptomatic people who are aged > 40 years and are overweight (BMI > 25) or obese (BMI > 30). However, a recent individual participant data (IPD) meta-analysis of 57 national surveys in LMIC showed that the risk of diabetes in people with BMI > 23 kg/m² was around 40% higher than in those with a BMI of 18.5-24.9 kg/m². In the same study, there was a notable increase in the prevalence of diabetes in men with BMI > 30 kg/m² who are aged 25 to 34 in sub-Saharan Africa. This trend was also observed in nearly all regions for those aged 35 and above. The authors, therefore, suggested screening for diabetes in people younger than 40 years, the cut-off lower than that currently recommended by WHO, in LMIC.[123]

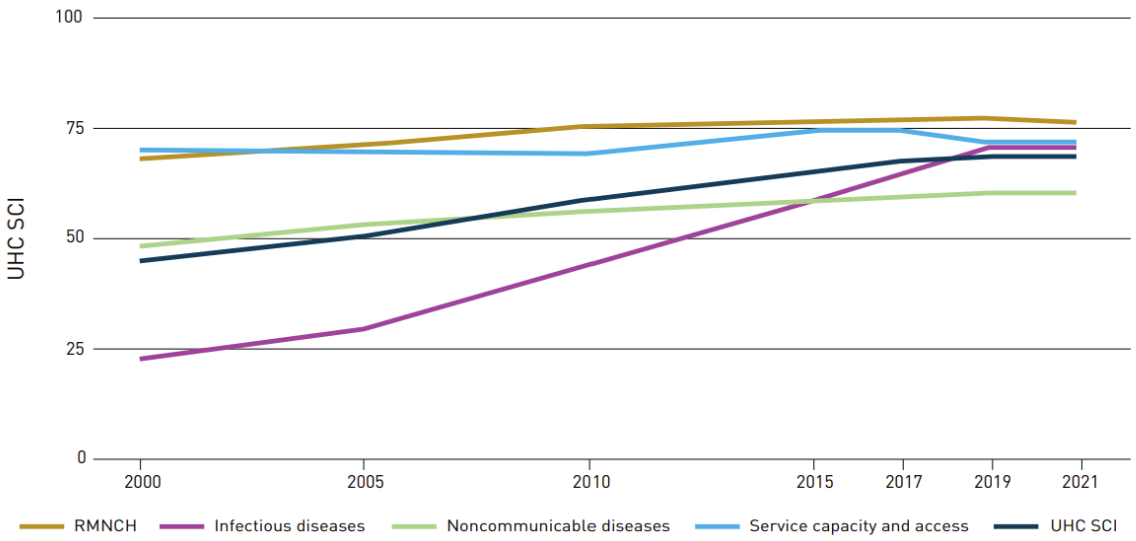
The management of hypertension and diabetes is a critical component of preventing CVD. WHO developed a model to predict the development of CVD over ten years to facilitate the risk assessment and the risk-tailored management of CVD risk factors.[124] WHO recommends the assessment of CVD risk using the prediction model in people with the following conditions: age > 40 years, smokers, obesity, hypertension, diabetes, or history of premature CVD, diabetes, or kidney disease in a first-degree relative.[124] In individuals with > 20% risk of CVD, WHO recommends statin in addition to addressing CVD risk factors such as unhealthy diet, smoking, hypertension, and harmful alcohol use.[121] However, the uptake of this recommendation in LMIC remains very poor. Based on nationally representative health surveys in 41 LMIC, only 8% were on statin for primary prevention among those eligible and 21.9% for secondary prevention.[125] The uptake was far below the WHO target of 50%, and no country but Iran achieved the target.

1.8. Strategies for integrated screening and care for TB and NCD

A call for integration of the prevention and control of NCD in existing health programmes

There is a concerted global effort to integrate NCD prevention and control in other health programmes. The Political Declaration at the first United Nations UN) High-Level Meeting on NCDs in 2011 committed to the integration of NCD prevention and control within sexual and reproductive health, maternal and child health, and HIV/AIDS.[126] The Political Declaration at the Third High-Level Meeting on NCD in 2018 further reaffirmed the commitment and highlighted the TB programme as an additional area for integration.[127] When assessing indicators to monitor progress toward universal health coverage (UHC), the coverage of essential health services for NCDs is not advancing at the same pace as other health programs (Figure 1-5).[128] Thus, it is vital to leverage the already established health systems to scale up the coverage of NCD services efficiently.

Figure 1-5.Tends in UHC service coverage index by sub-component



Note: Black line indicates composite index, UHC SCI (SDG 3.8.1); RMNCH, reproductive, maternal, newborn, and child health.

Reproduced from: Tracking universal health coverage: 2023 global monitoring report. Geneva: World Health Organization and International Bank for Reconstruction and Development / The World Bank; 2023. Licence: CC BY-NC-SA 3.0 IGO.
UHC SCI: universal health coverage service coverage index; RMNCH: reproductive, maternal, newborn, and child health
The plot shows slower progress in the global coverage of NCD services than other health services.

To facilitate the integration, in 2023, WHO published an implementation guide, “Integrating the prevention and control of noncommunicable diseases in HIV/AIDS, tuberculosis, and sexual and reproductive health programmes”.[129] According to this guide, “integration consists of the organization and management of health services so that people receive the care they need, when they need it, in ways that are user friendly, achieve the desired results and provide value for money.” There are various types of integration, three of which are highlighted in the guidance (Table 1-4).

Table 1-4.Types of integrated care

Functional	Administrative and support functions and activities (financial, medicines, management and information systems) structured and integrated for the primary process of service delivery
Service	Integration, coordination and organization of (mainly) clinical health services
Organizational	Coordination of organizations through contracts, strategic alliances, knowledge networks or mergers to deliver comprehensive services to a defined population

Reproduced from: Integrating the prevention and control of noncommunicable diseases in HIV/AIDS, tuberculosis, and sexual and reproductive health programmes: implementation guidance. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

This thesis focuses on integrating service delivery to establish models of care that holistically address multiple healthcare needs people have.

There are examples of successful NCD prevention and care integration within existing disease programmes in LMIC. In particular, in settings with high HIV burden, countries have accumulated experiences in integrating NCD and HIV services, capitalizing on the robust foundation of HIV programmes that already existed. The WHO implementation guide reports five case studies of integrating NCD and HIV programmes in African countries.[129] One of those in Uganda integrated screening for hypertension and diabetes into a community testing programme for HIV. This integration resulted in finding newly diagnosed people with diabetes and hypertension. Malawi started screening for hypertension in people with HIV on ART. As a result, the screening coverage for hypertension among people with HIV on ART increased from 45% in 2015 to 96% in 2018. Similarly, a scoping review published in 2022 identified 37 studies that investigated the integration of HIV and NCD care in Sub-Saharan Africa.[130] The review found that the integration could reduce duplication and fragmentation of services, thereby increasing the efficiency of service delivery and improving clinical and quality outcomes such as retention in care, patient satisfaction, and waiting time.[130] These studies found that integration can be feasible but also identified barriers and challenges. Barriers and challenges include limited funding and trained staff, increased workload and the reluctance of health care

workers to extend their work, shortage of medical supplies, and weak NCD programmes.[129,130]

Existing strategies for integrated screening and care for TB and NCD

The bidirectional association between TB and NCD and their tendency to overlap within individuals calls for strategies addressing both conditions in an integrated manner. An integrated approach can lead to better care and health outcomes for each.

Consequently, international organisations, including WHO and the UNION, set recommendations on the integrated management of TB and NCD. In 2011, WHO and the Union jointly published the “Collaborative Framework for Care and Control of Tuberculosis and Diabetes”. [131] The framework proposed nine collaborative activities, which recommended screening active TB patients for diabetes and diabetic patients for TB (i.e. bidirectional screening). Similarly, WHO recommends the assessment of nutritional status among people with TB.[132] There is further advocacy for integrating care approaches for other conditions such as smoking and COPD, heavy alcohol drinking, malnutrition, and mental illness in people with TB, although the practice is variable.[133] When implemented consistently, these strategies can help improve NCD and TB outcomes in people with TB. However, focusing on people who already have active disease has limited overall impact. It will not address NCD or risk factors in a much larger population of those without TB who are not engaged in care. The prevalence of TB is around 1% or less in even high TB burden countries.[134] To help prevent the future development of TB, TB-NCD integrated care needs to additionally focus on preventing or treating underlying NCD in at-risk populations that are not yet engaged in care. Data to inform policy and interventions is currently lacking.

1.9. Thesis rationale

1.9.1. A proposal for a holistic approach toward household contact investigations

In this thesis, I propose integrated screening within household contact investigations as an underutilized opportunity to expand integrated approaches toward TB and NCD.

Systematic screening for TB among household contacts of persons with TB has been recommended globally, but its uptake in LMIC varies.[1]
The deployment of community health workers can help increase the uptake of TB contact investigations and could also extend the reach of other health services.[118,135] However, the opportunity is underutilized. There is currently no global policy to recommend screening of contacts for diseases like diabetes, beyond TB and HIV.[136] The uptake and implementation of other adjunct screening, such as the 2013 WHO guidance on the assessment of nutritional status, is unknown.

1.9.2. Research gaps

In contrast to the numerous evidence on the utility of contact tracing for increasing TB case finding, there is currently limited data to support the value of comprehensive NCD screening among contacts of people diagnosed with active TB.[132] The RATIONS trial has shown that giving nutritional supplements to household contacts could reduce TB incidence by 39%.[137] It might similarly be possible that addressing other NCD risk factors, such as diabetes, can similarly reduce TB incidence, not only improving NCD-related outcomes.

This thesis will address the following research gaps.

1. Burden of NCD and their determinants within households affected by TB

TB is associated with social mixing; people with TB and their close contacts likely share risk factors for NCD and TB, resulting in disease clustering among household contacts.

Studies in the general population have reported NCD clustering among household members.[138,139] There appears to be a higher prevalence of NCD among household members of a person diagnosed with NCD. In a study in India, the prevalence of diabetes and pre-diabetes among individuals living with people with diabetes was almost 2-fold that of those not residing with patients.[139] However, few studies have examined such clustering of NCD and/or TB risk factors in household contacts of people with TB. Another study in India reported that nearly 40% of adult household contacts of people with TB had diabetes or pre-diabetes.[140] Another in South Africa reported that 17.4% of TB contacts had diabetes.[141] While those estimates were almost two times higher than the national prevalence of diabetes, the lack of a control group in these studies precluded direct comparison with members of households without a known TB source within the same geographical area, adjusting for known risk factors such as sex and age. There are no clinical studies that investigated the burden of various types of NCD among household contacts of people diagnosed with TB compared with suitable control neighbourhood households in the general community. Some studies examined the prevalence of diabetes among contacts, though without a control group; however, no systematic review synthesized their data. Household contacts of source TB patients may thus possibly have a higher burden of NCD than the general population, but this is currently not known.

2. *Association of NCD and NCD risk factors with subclinical-to-symptomatic spectrum of TB*

Data from TB prevalence surveys show that around 50% of people with TB are asymptomatic.[142] Thus, reliance on symptom-based screening will miss those with subclinical TB. Chest X-rays can help identify people with TB, but logistical constraints hamper universal X-ray screening. The WHO recommends systematic screening for active TB disease in specific populations with a higher prevalence of TB.[112]

NCD such as diabetes and NCD risk factors (e.g., smoking and alcohol use) are known to increase the risk of TB. Therefore, prioritizing TB screening in people with these conditions within households and communities may increase the effectiveness of screening programs. As discussed, NCD and their risk factors are often shared among household members. Identifying TB among people with NCD and their risk factors and extending TB investigation within their households might be an efficient approach to addressing the convergence of TB and NCD. However, it is unknown whether NCD and NCD risk factors can be used to identify people with different manifestations of TB.

3. Cost and cost-effectiveness of integrated NCD screening within household contact investigations

There is currently no data on the costs and cost-effectiveness of integrated NCD screening within household contact investigations. Assessing the economic implications of a new intervention is a key element in making public health recommendations. Furthermore, understanding the drivers of cost-effectiveness for integrated NCD screening can help tailor the approach to optimize its cost-effectiveness.

2. Aim and Objectives

2.1. Aim

I aimed to use mixed quantitative approaches to derive data that contribute to the understanding of NCD multimorbidity in households affected by TB in LMIC. The evidence derived will address the dearth of data, advance knowledge, inform public health policy and design of novel multifaceted clinical and socio-economic interventions for TB and associated multimorbidity care and prevention.

Figure 2-1 presents an overview of my PhD research.

2.2. Objectives

1) To determine, through individual patient meta-analyses, the prevalence and determinants of NCD multimorbidity among members of households with TB compared to control households

Hypothesis: Household contacts of TB patients have a high burden and risk of non-communicable multimorbidity and risk factors compared to control households in the same neighbourhood.

2) To quantify the proportion of subclinical TB using the standardised definition and investigate the risk of symptomatic and subclinical TB in people with NCDs and NCD risk factors compared to those without such factors.

Hypothesis: The risk of symptomatic and subclinical TB differs by the presence of NCD and NCD risk factors; they can be used to identify individuals who should be prioritised for systematic TB screening.

3) To characterise the clinical pattern of multimorbidity among household contacts of people diagnosed with TB and determine the yield of systematic integrated screening for TB infection, NCD and related risk factors compared to control households

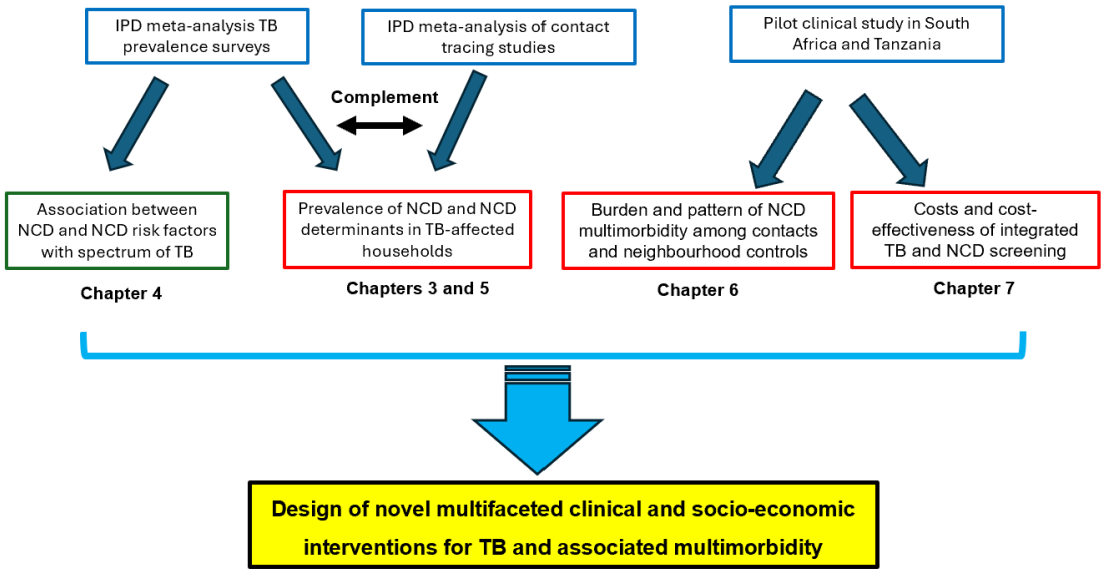
Hypothesis: In the context of high TB and HIV/AIDS, household contacts of TB patients have a unique pattern and high burden of TB-associated multimorbidity

compared to control households; systematic disease screening identifies priorities for intervention.

4) To estimate the magnitude and type of individual and household costs associated with TB-NCD multimorbidity and model the potential cost-effectiveness of integrated TB-NCD screening within contact tracing activities compared to TB screening alone

Hypothesis: Households with TB and NCD multimorbidity face additional financial burdens than households with TB alone; integrated TB-NCD screening is more cost-effective than TB screening alone by improving quality of life and reducing illness and deaths.

Figure 2-1.Overview of my PhD research



3. Prevalence of non-communicable diseases and their risk factors in households affected by tuberculosis: an individual participant data meta-analysis of national tuberculosis prevalence surveys from 16 countries

3.1. Abstract

Background

TB and NCD have a bidirectional association and share predisposing risk factors. TB-associated NCD might cluster within households affected with TB due to shared risk factors, which would support integrated household-wide screening and interventions.

I conducted an IPD meta-analysis of national TB prevalence surveys to determine the prevalence of NCD and NCD risk factors in members of households with TB in comparison with members of households without TB.

Method

I identified eligible surveys that reported at least one NCD or NCD risk factor through the archive maintained by the World Health Organization and searching in Medline and Embase from 1 January 2000 to 10 August 2021, which was updated on 23 March 2023. I described the prevalence of NCD and their risk factors among people who do not have TB living in households with at least one person with TB (members of households with TB), and compared them with members of households without TB.

Results

I included 16 surveys (n = 740,815) from Asia and Africa. Across surveys, 3.0% of members of households with TB had a self-reported diabetes, and 22.3% were smokers. In a multivariable model adjusted for age and gender, the odds of smoking was higher among members of households with TB (adjusted odds ratio (aOR) 1.23; 95% CI: 1.11- 1.38), compared with members of households

without TB. The analysis did not find a significant difference in the prevalence of alcohol drinking, diabetes, hypertension, or BMI between members of households with and without TB. The prevalence of diabetes and hypertension was low due to reliance on self-report, suggesting a gap in their diagnosis.

Conclusion

The review found a higher prevalence of smoking in members of households with TB than in households without a person with TB. Data on NCD diagnosed using objective diagnostic methods were lacking. A well-designed prospective study with systematic NCD screening among TB contacts is necessary to accurately assess the burden of NCDs and their risk factors.

3.2. Introduction

There is limited data on the prevalence of NCD and NCD risk factors among household contacts of people with TB compared to the general population (highlighted in section 1.8). It is not known whether NCD cluster in households affected by TB. In national TB prevalence surveys, participants are invited per household; thus, their data from prevalence surveys allow me to examine the burden of NCD and NCD risk factors in households affected by TB, and compare them to households without an individual diagnosed with TB.

I, therefore, conducted a systematic review and IPD meta-analysis of national TB prevalence surveys to understand if NCD and NCD risk factors cluster in members of households with TB. I also aimed to identify predictors for NCD and NCD risk factors in members of households with TB.

3.3. Methods

The protocol of this systematic review has been pre-registered. (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=272679)

3.3.1. Search strategy and eligibility criteria

I included national and sub-national TB prevalence surveys in LMIC that reported data on at least one NCD or NCD risk factor (e.g., smoking, alcohol use).

In general, national TB prevalence surveys adapt a standard protocol recommended by the WHO.[143] The surveys enrol individuals aged 15 years and above, identified through a multi-stage random sampling process. Participants receive symptom screening and a chest X-ray. Participants displaying symptoms or chest X-rays suggestive of TB (or any lung abnormalities, as specified by each survey) provide sputum samples for confirmatory TB testing.

I included surveys that collected at least one of the followings: diabetes, hypertension, CKD, CVD, chronic respiratory disease, smoking, harmful use of

alcohol, and malnutrition (based on BMI or as defined by surveys). The surveys' own definitions were used to diagnose NCDs.

For the diagnosis of TB disease, I used survey cases as defined in each survey,[143] which were confirmed bacteriologically either by culture or Gene Xpert.

I selected eligible prevalence surveys from the WHO's comprehensive list of national surveys.[144] To determine survey eligibility, I reviewed their reports and protocols. In addition, a systematic search was conducted in the Medline (OVID) and Embase databases on August 10, 2021, aiming to find sub-national surveys published after January 1, 2000. Tables 3-1 and 3-2 present the detailed search strategies.

Table 3-1. Medline search strategy

1	tuberculosis.m_titl.
2	prevalence.m_titl.
3	survey.tw.
4	1 and 2 and 3
5	limit 4 to yr="2000 -Current"

Table 3-2. EMBASE search strategy

1	tuberculosis.m_titl.
2	prevalence.m_titl.
3	survey.ti,ab,kw.
4	1 and 2 and 3
5	limit 4 to yr="2000 -Current"

I and another investigator independently reviewed titles and abstracts to identify potentially eligible studies in duplicate. Both of us reviewed full-text articles of those identified through the first screening. Discrepancies were resolved through discussion.

3.3.2. Data collection and quality assessment

National TB programmes or equivalents or authors of the eligible surveys were invited to participate and share IPD (See Table 3-3 for the list of variables).

Table 3-3.List of variables that were requested

Household level information
Cluster ID
Household ID
Availability of assets (e.g. refrigerator)
Access to clean water
Use of biomass fuel
Number of rooms
Household Income
Other variables relevant to socioeconomic status collected in surveys.
Number of household members
Education status
Individual data
Sex
Age
Household id
Smoking
Alcohol use
HIV status
Body weight
Body mass index
Occupation
Education level
Diabetes
Hypertension
Silicosis
Chronic obstructive pulmonary disease
Asthma
Past history of TB
Current TB treatment
Symptoms
Chest X-Ray abnormality
Smear microscopy result
Xpert MTB/RIF result

Sputum Culture result

I verified the data against the reports of each survey, addressing any discrepancies by reaching out to the original investigators. The categorisation of alcohol consumption frequency varied across surveys (as shown in Table 3-4). Based on these varying definitions, I pragmatically grouped alcohol consumption into three categories: drinking ≥ twice per week, once a week or less, vs no drinking. Similarly, smoking history was classified into current smoking, past smoking, and never smoking.

Table 3-4.Categorisations of current alcohol drinking by surveys

Eswatini	None Once a week Monthly or less 2-4 times a month 2-3 times a week 4 or more times a week
Gambia	None Occasionally 1-2 times/wk 3-5 times/wk > 5 times/wks
Ghana	None Once in past year Once in 6 months Once in a month Once in a week 3-4 times a week Everyday
Mongolia	None Once a month or less 2-4 times a month 2-3 times a week At least 4 times a week
Mozambique	None 1 times a month or less 2 to 4 times a month 2 to 3 times a week 4 or more times a week
Namibia	How many days have you consumed alcohol in the past two weeks? None 1-2 3-4 5+
South Africa	None Once a month or less 2- 4 times a month 2-3 times a week 4 or more times a week
United Republic of Tanzania	None Sporadic Monthly Weekly Daily

Other countries did not collect data on alcohol drinking.

3.3.3. Outcome

The outcome was the prevalence of a priori-determined NCD or NCD risk factors. These were diabetes, hypertension, CKD, CVD, chronic respiratory disease, smoking, harmful use of alcohol, and BMI. The outcomes were compared between people with TB, members of households with TB, and members of households without TB. To define TB cases, I used survey cases as defined in each survey, which were confirmed bacteriologically either by culture or Gene Xpert.[143]

3.3.4. Quality assessment

I assessed the quality of the included surveys by assessing the participation rate (the risk of selection bias), methods for screening and diagnosis of active TB (the risk of misclassification of TB status), and methods for NCD diagnosis (the risk of misclassification of TB status). For NCD risk factors, all surveys assessed smoking and alcohol status based on participants' self-report and heights and weights were actually measured.

3.3.5. Statistical analysis

Handling of missing data

Not all outcome variables were collected in all surveys. Therefore, I identified a set of surveys that collected data on each outcome and performed multiple imputation separately for each outcome, restricting to those surveys with data. To address sporadic missingness in each outcome, I conducted multiple imputation using multilevel fully conditional specifications. The main predictor, TB status, was classified into three groups: people with TB, members of households with TB, and members of households without TB. The imputation models included NCD and their risk factors, TB status, age, gender, TB symptoms, and chest x-ray findings. BMI was included after transformation and then imputed (i.e. so-called 'just another variable' approach).[145] Because the number of surveys reporting most outcomes was small, the model included fixed intercepts for surveys. Sampling clusters were included as random intercepts.

I generated 20 multiply imputed data sets with 20 iterations between successive imputations. I assessed model convergence visually using trace plots. All primary

analyses were performed across multiply imputed datasets; substantive models were fitted on each imputed dataset, and their outputs were combined using Rubin's rules.

Comparison of prevalence of NCD between members of households with TB and members of non-TB households

I presented the proportion of participants with NCD and NCD risk factors, stratified into three groups: people with TB, people who do not have TB in households with at least one person with TB (referred to as members of households with TB), and members of households without TB). I performed a multilevel logistic regression analysis to estimate the odds ratios for NCD and NCD risk factors, comparing members of households with TB and those without TB. For this analysis, alcohol drinking was dichotomised into ≥ twice per week vs < twice per week, because a multinominal model failed to converge. The model included random intercepts for sampling clusters and fixed intercepts for surveys. Next, I examined the odds ratio for NCD and NCD risk factors, adjusting for age and gender of participants. The analysis did not intend to examine causal associations; instead, my main objective was simply to ascertain the overall increase in the prevalence of NCD/NCD risk factors in members of households with TB compared to those without TB who are of the same age and gender. While various factors could contribute to this increase, they were not considered since any observed rise, irrespective of the causes, suggests a potential need for intervention.

I assessed the heterogeneity of the estimates using forest plots; the proportion of total variability due to between-study heterogeneity was quantified by calculating I-squared. Further, I conducted a sub-group analysis by region to examine differences in associations by region.

Association between characteristics of people with TB and NCD and their risk factors among household members

I examined if the characteristics of people with TB were associated with the presence of NCD or NCD risk factors among their household members. Variables of interest were the presence of NCD and their risk factors among people with TB, age, and gender. I first fitted a multilevel logistic regression model including NCD/risk factor status, age, and gender of people with TB without age and gender of their

household members to identify predictors of NCD and NCD risk factors based on characteristics of people with TB.

Identifying such predictors would prioritise NCD screening among contacts of index cases with specific risk factors. Next, I fitted the same model, including age and gender of the household members, to identify predictors at the individual level rather than the household level based on the characteristics of people with TB in the household. When households included multiple people with TB, I randomly sampled one person with TB per household, and their characteristics were used in the models (variation due to random sample is reflected in confidence intervals).

Publication bias was not expected and hence was not assessed since WHO has a complete archive of national TB prevalence surveys to date.

Sensitivity analysis

First, I repeated the analysis using an alternative categorisation of alcohol drinking: any drinking vs no drinking. Second, I repeated the analyses by excluding countries that collected NCD data only among a subset of the participants.

Third, I conducted a record-level quantitative bias analysis to explore the impact of the misclassification of diabetes and hypertension status.[146] This involved creating hypothetical datasets, adjusting for potential misclassification biases at various sensitivity and specificity levels, and applying multivariable regression models to these adjusted datasets.[146] This approach contrasts with the summary-level quantitative bias analysis, which relies on data aggregated into a contingency table. The summary-level quantitative bias analysis can be implemented without individual data, such as data reported in published papers, and requires less computing time; however, it is unable to accommodate complex analytic models (e.g. multiple variable regressions). I, therefore, performed the record-level analysis.

I assumed various levels of accuracy (i.e. sensitivity and specificity) of diabetes and hypertension status, testing both non-differential and differential misclassification by TB status. Based on the literature, I varied the sensitivity of self-reported diabetes and hypertension between 40% to 80%.[147-150] The prevalence of self-reported diabetes in the study population was 2.8% in people without TB (see Results). This

suggests a high specificity of diabetes in the study population, which is consistent with the literature.[147,148] For hypertension, I tested a specificity of 85%, 90%, and 95%.[149,150] I adapted the approach described by Fox et al. while using fixed levels of sensitivity and specificity.[146] I first sampled one of the 20 multiply imputed datasets and estimated positive and negative predictive values for diabetes/hypertension, given their observed status. Second, using the predictive values, I simulated a new variable representing the true diabetes/hypertension status drawing at random from a Bernoulli distribution. I fitted a logistic regression model using the new variable as an outcome and TB status as a predictor, adjusted for age and gender. Finally, to account for random errors, I sampled a standard normal deviate, multiplied it by the standard error of the bias-adjusted association, and combined it with the point estimate from the model. I repeated the above process 1000 times and presented the median and 2.5th and 97.5th percentiles as uncertainty intervals. To reduce the computation time, the regression model excluded random intercepts for clusters, unlike the model used in the primary analysis. To compare the results between models that are comparable, I compared the results of this sensitivity analysis with those from the models using observed diabetes and hypertension status without random intercepts for clusters.

3.3.6. Ethics

This IPD meta-analysis was approved by the UCL Research Ethics Committee (18969/001). All participants provided informed consent to participate in the primary surveys included in this meta-analysis.

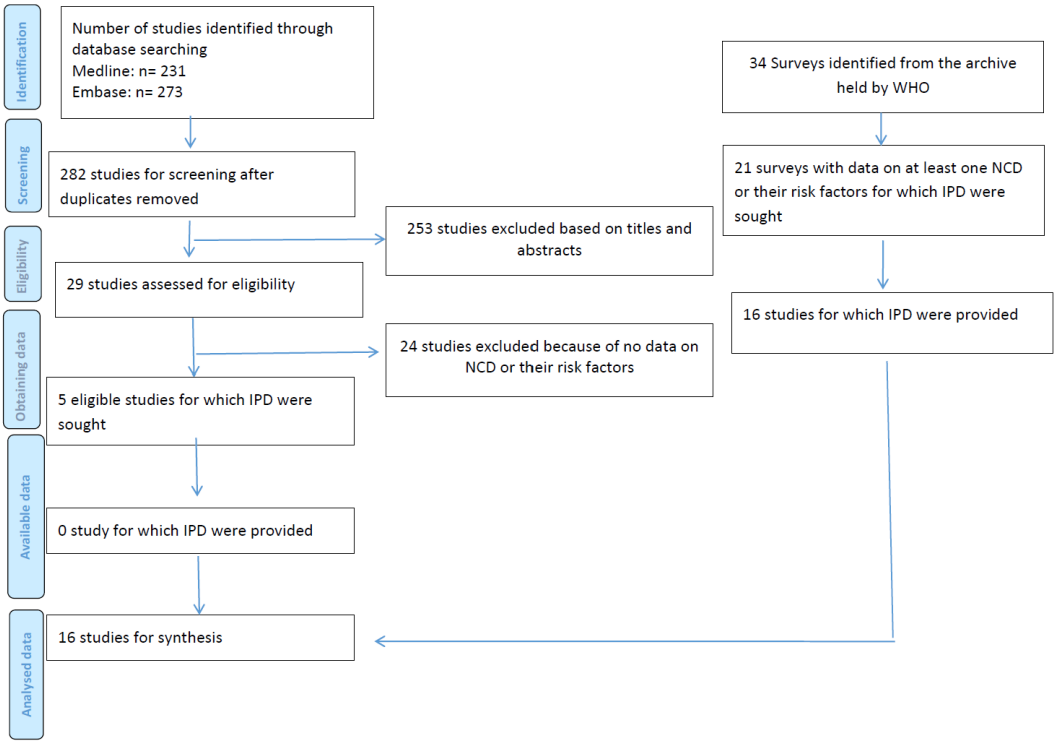
3.4. Results

3.4.1. Search results and overall characteristics

From 21 eligible surveys found through the WHO archive, I received IPD from 16 surveys (n=740,815) (Figure 3-1).[151-166] The remaining five surveys (in the Democratic People's Republic of Korea, Ethiopia, Myanmar, Rwanda, and Zimbabwe) did not provide data; reasons were not provided. I included 16 out of 21 eligible national surveys for smoking, nine out of 11 for diabetes (n = 427,922),[151-157,164,166] eight out of 10 for alcohol (n = 327,021),[152,154-157,162,164] four of four for BMI (n = 174,437), [152,155,156,158] and two of two for hypertension (n = 79,804).[152,155] The

database searches identified additional five eligible studies, all reporting only smoking status[167-171]; none of the studies responded to our request for IPD before the closure of data collection. All were sub-national surveys, including 286,340 participants and only collected data on smoking.

Figure 3-1. Study selection



I included surveys conducted between 2012 and 2020, five in Asia and 11 in Africa (Table 3-5). All participants were aged 15 years or older. The survey participation rate ranged from 56.8 to 90.9% (median: 77.2%) (Table 3-6). In all surveys, there were fewer male participants than females (from 38.0 to 46.6%). In three surveys in which information was sought from all participants, the proportion of participants with diabetes ranged from 2.4 to 5.1%. The median number of participants per household was two persons (interquartile range: 1-3). I did not find issues that could undermine IPD integrity.

In all surveys, diabetes was based on self-reports (Table 3-6). For hypertension, one survey used a combination of blood pressure measurements[152] and self-reports and the other used self-reports.[155] Five surveys collected data on NCD and/or their risk factors from a subset of participants: participants eligible for sputum collection and a

randomly selected subset of other participants in Eswatini, Namibia, and Mozambique,[157,165] those eligible for sputum collection in the United Republic of Tanzania, and Viet Nam,[156,166] and participants who had cough ≥ two weeks, had TB diagnosis, or treatment history in Ghana (Table 3-5 and Figure 3-2).[154]

Table 3-5.Characteristics of participants by survey

	group	Bangladesh	Eswatini	Gambia	Ghana	Indonesia	Lesotho	Malawi	Mongolia	Mozambique	Namibia	Nigeria	Philippines	South Africa	UR Tanzania	Uganda	Viet Nam
	Year	2015-16	2019	2012	2013	2013-14	2019	2013-14	2014-15	2017-2020	2018	2012	2016	2017-2019	2012	2014-15	2017-18
Age	Median (IQR) years	33 (23-46)	32 (21-48)	28 (20-41)	35 (23-50)	37 (26-50)	37 (24-56)	30 (21-44)	39 (28-52)	29 (20-44)	34 (23-48)	32 (23-48)	37 (24-52)	37 (25-55)	35 (23-50)	29 (21-42)	47 (33-58)
	N	98710	24358	43099	61724	67942	21719	31579	50309	32445	29495	44186	46689	35191	50418	41154	61763
Gender	Male, n (%)	44365 (44.9%)	9939 (40.8%)	17504 (40.6%)	24688 (40.0%)	31632 (46.6%)	8597 (39.6%)	13099 (41.5%)	20070 (39.9%)	14001 (43.2%)	12595 (42.7%)	18178 (41.1%)	20893 (44.7%)	13388 (38.0%)	20735 (41.1%)	17485 (42.5%)	27150 (44.0%)
	N	98710	24358	43100	61726	67944	21719	31579	50309	32445	29495	44186	46689	35191	50436	41154	61763
Smoking	Current smoker	21416 (21.7%)	667 (8.2%)	4961 (11.5%)	152 (5.4%)	23025 (33.9%)	5848 (27.0%)	3031 (9.6%)	12291 (24.5%)	1337 (10.7%)	2196 (18.1%)	2139 (4.8%)	10749 (23.1%)	9367 (26.7%)	875 (14.6%)	3020 (7.3%)	1459 (32.2%)
	N	98710	8105	43100	2819	67944	21648	31579	50096	12520	12112	44185	46514	35117	6002	41147	4532
Alcohol	No drinking, n (%)	NA	6632 (82.4%)	42655 (99.0%)	1856 (65.8%)	NA	NA	NA	27149 (54.4%)	10248 (81.7%)	7086 (67.4%)	NA	NA	23323 (66.3%)	3744 (62.5%)	NA	NA
	Weekly or less, n (%)	NA	991 (12.3%)	371 (0.9%)	570 (20.2%)	NA	NA	NA	22616 (45.3%)	1938 (15.4%)	2028 (19.3%)	NA	NA	9858 (28.0%)	1166 (19.4%)	NA	NA
	Twice per week or more, n (%)	NA	427 (5.3%)	59 (0.1%)	393 (13.9%)	NA	NA	NA	129 (0.3%)	362 (2.9%)	1399 (13.3%)	NA	NA	2010 (5.7%)	1085 (18.1%)	NA	NA
	N	NA	8050	43085	2819	NA	NA	NA	49894	12548	10513	NA	NA	35191	5995	NA	NA
Diabetes	Diabetes, n (%)	NA	231 (3.8%)	NA	103 (3.9%)	1654 (2.4%)	NA	NA	1235 (2.5%)	NA	183 (1.5%)	NA	1866 (4.0%)	1784 (5.1%)	61 (1.0%)	NA	376 (8.3%)
	N	NA	6005	NA	2631	67944	NA	NA	50305	NA	11897	NA	46689	34651	5990	NA	4530
HIV	Positive, n (%)	NA	1674 (30.9%)	NA	NA	NA	3915 (23.0%)	1840 (9.3%)	75 (0.1%)	2966 (13.0%)	3338 (13.7%)	NA	NA	4606 (17.4%)	307 (5.1%)	422 (9.6%)	NA
	N	NA	5415	NA	NA	NA	17031	19703	50306	22845	24391	NA	NA	26406	6002	4394	NA
Hypertension	Hypertension, n (%)	NA	NA	NA	NA	NA	NA	NA	19990 (40.4%)	NA	1851 (15.6%)	NA	NA	NA	NA	NA	NA
	N	NA	NA	NA	NA	NA	NA	NA	49495	NA	11897	NA	NA	NA	NA	NA	NA
BMI	Mean (SD) kg/m^2	NA	NA	NA	NA	NA	NA	NA	26.1 (5.0)	NA	23.1 (5.3)	23.8 (4.8)	NA	NA	21.8 (4.2)	NA	NA
	N	NA	NA	NA	NA	NA	NA	NA	48239	NA	10827	40673	NA	NA	5796	NA	NA
Active TB	Active TB, n (%)	278 (0.3%)	70 (0.3%)	77 (0.2%)	202 (0.3%)	426 (0.6%)	132 (0.6%)	132 (0.4%)	248 (0.5%)	89 (0.3%)	119 (0.4%)	233 (0.5%)	466 (1.1%)	234 (0.7%)	159 (0.3%)	160 (0.4%)	221 (0.4%)

	N	98541	23331	42588	61541	67625	21083	31463	49496	29697	27921	42766	44333	33700	49485	40851	61329

TB: tuberculosis; IQR' interquartile range; SD: standar

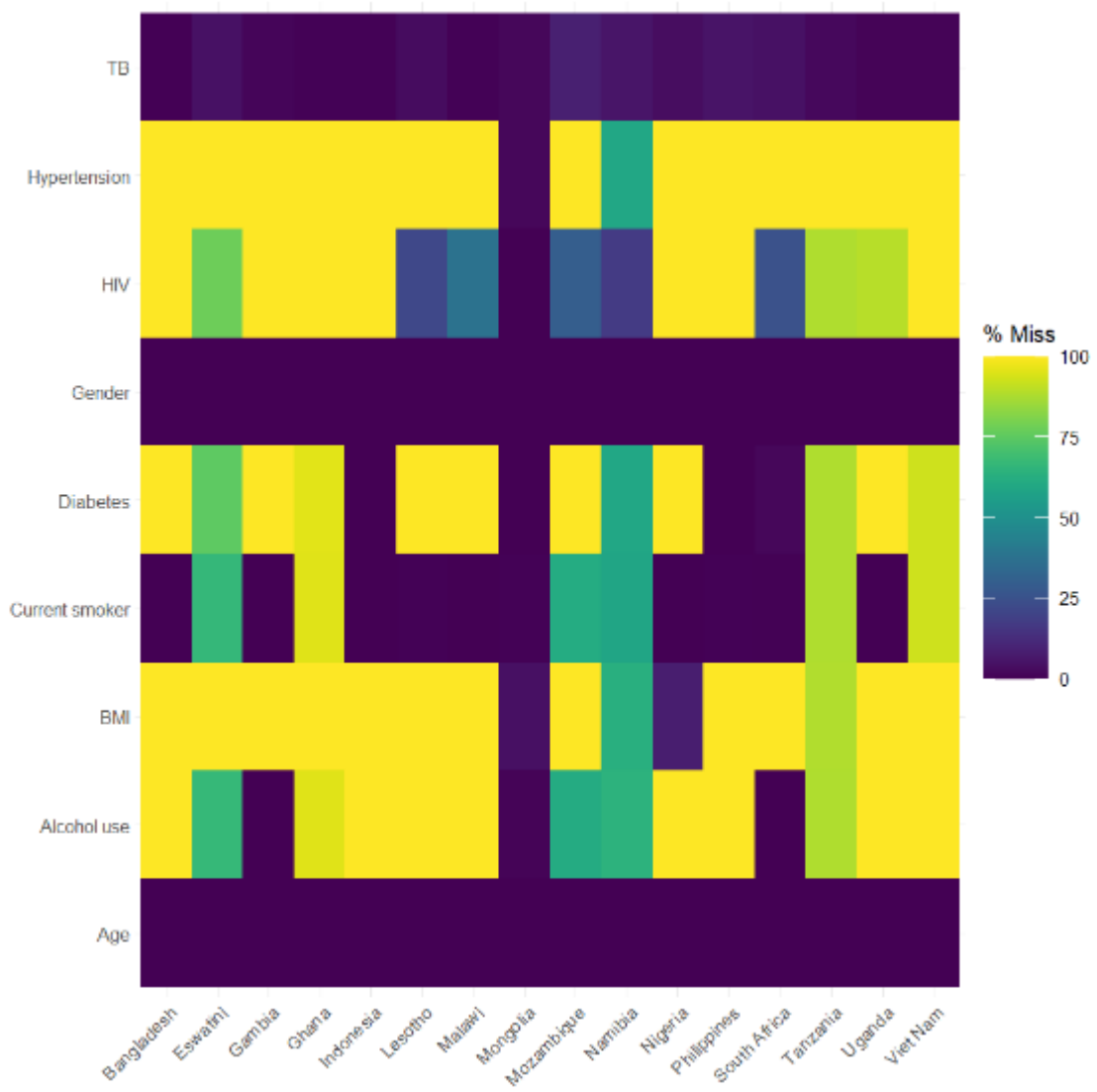
Table 3-6. Quality of individual surveys

Survey	Selection	Measurement of the exposure (TB status)			Measurement of the outcomes		Missing data
	# participated/# eligible (%)	Symptom screening criteria	Chest x-ray criteria	Diagnostic method	Diagnosis of diabetes	Diagnosis of hypertension	NCD data sought in all participants?
Bangladesh	98710/108834 (90.7)	Scoring based on cough, haemoptysis, weight loss, fever, and/or night sweats	Any lung abnormality	Smear, culture, and Xpert	NA	NA	Yes
Eswatini	24358/NA (NA)	Cough of any duration, fever for ≥ 2 weeks, unexplained weight loss ≥ 2 weeks, and/or night sweats ≥ 2 weeks	Any lung abnormality	Xpert. Culture on Xpert positive samples	Self-report	NA	In participants eligible for sputum collection and a randomly selected subset of the others.
Gambia	43100/55832 (77.2)	Cough ≥ 2 weeks, Cough < 2 weeks with ≥ 2 other TB symptoms*, or No cough with ≥ 3 other TB symptoms*	Any lung or mediastinum abnormality	Smear and Culture. Xpert for survey TB cases	NA	NA	Yes
Ghana	61726/67757 (91.1)	Cough ≥ 2 weeks	Any lung abnormality	Smear and Culture. Xpert on smear+ samples, and if cultures contaminated	Self-report	NA	In participants who had cough ≥ 2 weeks, TB diagnosis, or treatment history
Indonesia	67944/76576 (88.7)	Cough ≥ 2 weeks and/or haemoptysis	Any lung or pleura abnormality	Smear and Culture. Xpert on smear+ and non-conclusive culture samples	Self-report	NA	Yes
Lesotho	21719/26857 (80.9)	Cough ≥ 2 weeks, fever, weight loss, and/or night sweats	Any lung abnormality	Xpert and culture	NA	NA	Yes
Malawi	31579/39026 (80.9)	Any symptoms** ≥ 1 week	Any lung abnormality	Smear and Culture. Xpert on smear+ or if culture contaminated	NA	NA	Yes
Mongolia	50309/60031 (83.8)	Cough ≥ 2 weeks	Any lung abnormality	Smear and Culture, Xpert on smear+ samples	Self-report	Blood pressure measurement and self-report	Yes
Mozambique	32445/43442 (74.7)	Cough ≥2 weeks, blood in sputum, and/or any cough with one of the five symptoms/signs for ≥ 2 weeks***	Any lung or mediastinum abnormality or CAD4TB score ≥ 40	Smear, Xpert, and Culture	NA	NA	In participants eligible for sputum collection and a randomly selected subset of the others.
Namibia	29495/38353 (76.9)	Cough, night sweats, fever, and/or weight loss	Any lung abnormality or CAD4TB score ≥60	Smear, Xpert, and Culture	Self-report	Self-report	In participants eligible for sputum collection and a randomly selected subset of the others.
Nigeria	44186/77707 (56.8)	Cough ≥ 2 weeks	Any lung abnormality	Smear, culture, and Xpert	NA	NA	Yes
Philippines	35191/53250 (66.1)	Cough ≥2 weeks, blood in the sputum, and/or haemoptysis	Any lung abnormality	Smear and Culture	Self-report	NA	Yes
South Africa	46689/61466 (76)	Any cough, fever, night sweats, and/or weight loss	Any TB suggestive abnormality	Xpert Ultra and culture	Self-report	NA	Yes

United Republic of Tanzania	50447/65664 (76.8)	Cough ≥ 2 weeks, haemoptysis, fever ≥2 weeks, weight loss, and/or night sweats	Any lung (or mediastinum) abnormality	Smear, culture, and Xpert A concern raised about the validity of the number of bacteriologically positive cases.	Self-report	NA	In participants eligible for sputum submission
Uganda	41154/45293 (90.9)	Cough ≥ 2 weeks	Any lung abnormality	Smear and culture. Xpert on smear+ samples	NA	NA	Yes
Viet Nam	61763/87207 (70.8)	Productive cough ≥ 2 weeks	Any lung abnormality	Smear and culture	Self-report	NA	In participants eligible for sputum submission

*Chest pain, night sweats, shortness of breath, loss of appetite, weight loss, fever, haemoptysis.
**Cough, sputum production, haemoptysis, chest pain, weight loss, night sweats, fatigue, fever, and shortness of breath.
***Chest pain, unexplained fever, night sweats, weight loss, and low mid-upper arm circumference

Figure 3-1.Proportion of missing data by variable and survey



TB: tuberculosis; HIV: human immunodeficiency virus; BMI: body mass index

Table 3-7 presents the characteristics of participants who were classified into three groups: people with TB, those in the same households as people with TB, and those living in households without TB. The median age was higher in people with TB at 44 years (interquartile range (IQR): 32-60) than in members of households with TB (median 34; IQR 22-50) and those without TB (median 35 years; IQR 24-50). A majority of people with TB were male (63.8%), while those in the other two groups were less likely to be male (40.0% in members of households with TB and 42.4% in those without TB). The diabetes prevalence was 5.6% in people with TB compared to 3.0% in members of households with TB and 3.2% in those without TB.

Table 3-7.Demographic and clinical characteristics of study participants

	Group	Members of households without TB	Members of households with TB	People with TB
Age	Median (IQR) years	35.0 (24-50)	34 (22-50)	44 (32-60)
	N	688767	7082	3245
Gender	Male, n (%)	291746 (42.4%)	2831 (40.0%)	2071 (63.8%)
	N	688788	7082	3246
Alcohol	No drinking, n (%)	109961 (72.9%)	1053 (68.5%)	616 (58.6%)
	Weekly or less, n (%)	35873 (23.8%)	409 (26.6%)	321 (30.5%)
	Twice per week or more, n (%)	5026 (3.3%)	75 (4.9%)	115 (10.9%)
	N	150860	1537	1052
BMI	Mean (SD) kg/m^2	24.7 (5.1)	24.3 (5.0)	21.4 (4.4)
	N	94000	1342	728
Smoking	Current smoker	95093 (19.5%)	1218 (22.3%)	1150 (36.8%)
	N	487397	5471	3121
Diabetes	Diabetes, n (%)	6684 (3.2%)	86 (3.0%)	112 (5.6%)
	N	209910	2875	2018
HIV	Positive, n (%)	16856 (10.6%)	130 (9.1%)	241 (21.2%)
	N	159274	1424	1136
Hypertension	Hypertension, n (%)	20353 (36.2%)	190 (33.4%)	91 (25.6%)
	N	56228	569	355

Note: Raw data before imputation. Denominators (N) vary by variables because of missing data.
BMI: body mass index; IQR: interquartile range; SD: standard deviation

3.4.2. Prevalence of NCD and NCD risk factors in members of households with TB compared to members of households without TB

In the univariable model, members of households with TB were slightly more likely to smoke than members of households without TB (OR 1.12, 95% CI 1.05-1.20) (Table 3-8). When adjusting for age and gender, the odds of smoking were higher among members of households with TB (aOR 1.23, 95% CI 1.11- 1.38) compared with members of households without TB. The estimated aOR ranged from 0.87 to 1.78, with the highest observed in South Africa (I-squared = 35.4%, p = 0.15, $tau^2 = 0.01$) (Figure 3-3). The higher prevalence of smoking among members of households with TB was observed both in Asian and African countries, and there was no significant difference by region (p = 0.0751) (Figure 3-4).

For alcohol drinking, there was no evidence that it was more common in members of households with TB (aOR 1.19; 95% CI 0.95-1.47) (Table 3-8 and Figure 3-5).

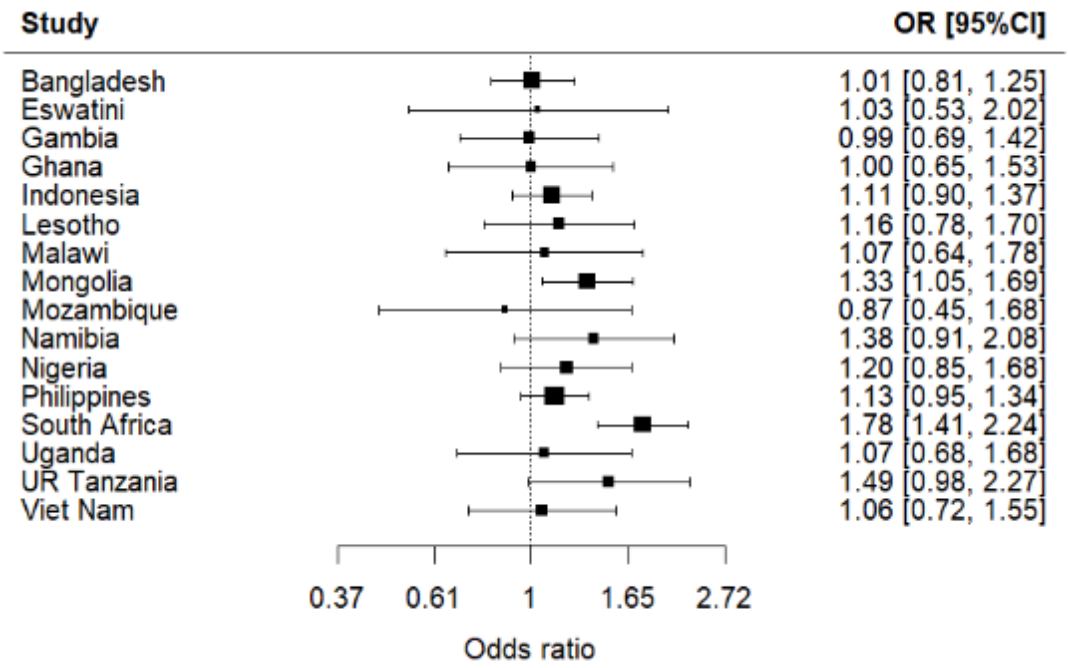
I did not find evidence that the prevalence of diabetes or hypertension differed between members of households with and without TB (Tables 3-8 and Figures 3-6 and 3-7). Likewise, the mean BMI was not different between members of households with TB and those without TB (adjusted difference -0.13, 95% CI -0.48; 0.21) (Table 3-4 and Figure 3-8).

Table 3-8.Prevalence of NCD/NCD risk factors in members of households with TB compared to those without TB

	Current smoker	**Alcohol drinking twice per week or more**	**Diabetes**	**Hypertension**	**BMI**
Group	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	Difference (95%C)
Member of households without TB (Reference)	1	1	1	1	-
Members of households with TB (unadjusted)	1.12 (1.05-1.20), p = 0.0013	1.18 (0.96-1.46), p = 0.1223	0.90 (0.74-1.10), p = 0.3013	0.91 (0.76-1.08), p = 0.2681	-0.10 (-0.45; 0.25), p = 0. 5772
Members of households with TB (Adjusted for age and gender)	1.23 (1.11- 1.38), p = 0.0003	1.19 (0.95-1.47), p = 0.1222	0.94 (0.77-1.15), p = 0.5333	0.88 (0.73-1.06), p = 0.1772	-0.13 (-0.48; 0.21) , p = 0.4431

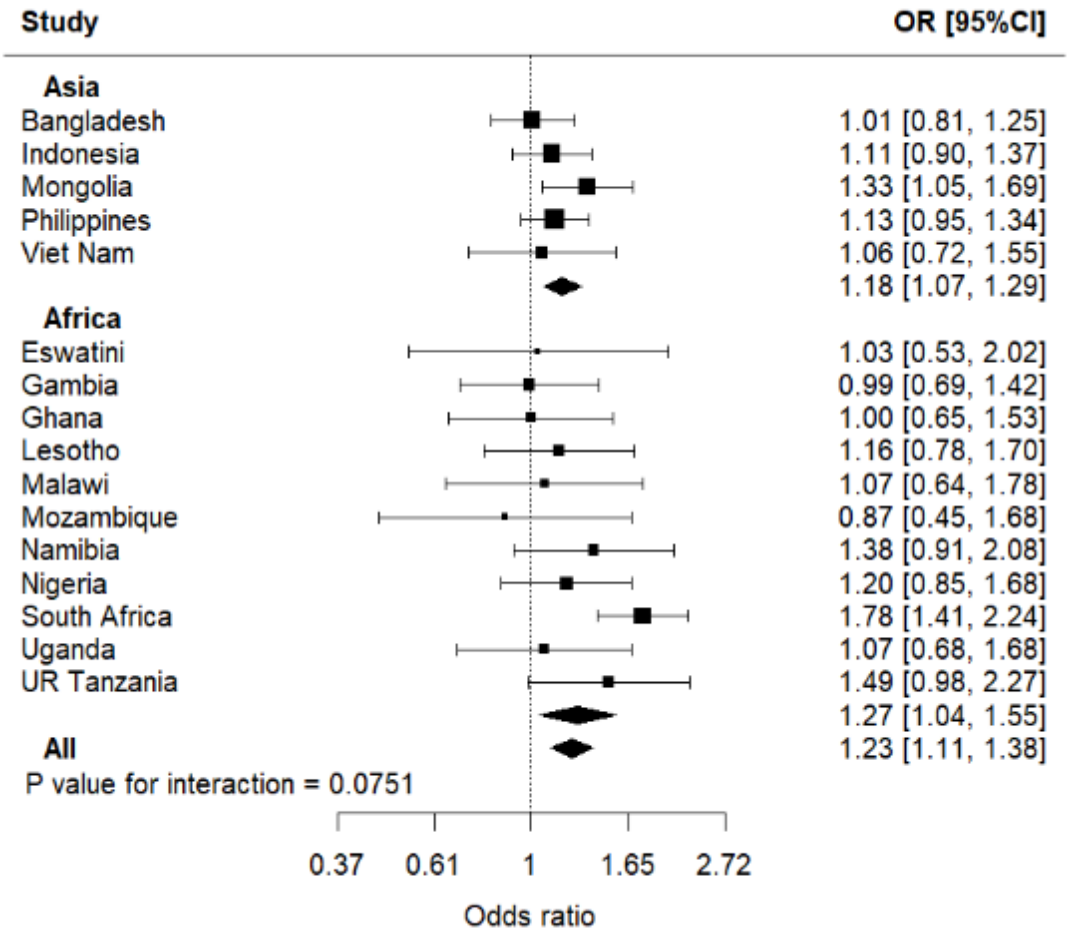
Note: The estimates were from mixed-effects regression models accounting for clustering within surveys and sampling clusters.
OR: odds ratio; CI: confidence interval; BMI: body mass index

Figure 3-2.Current smoking in members of households with TB compared to those without TB



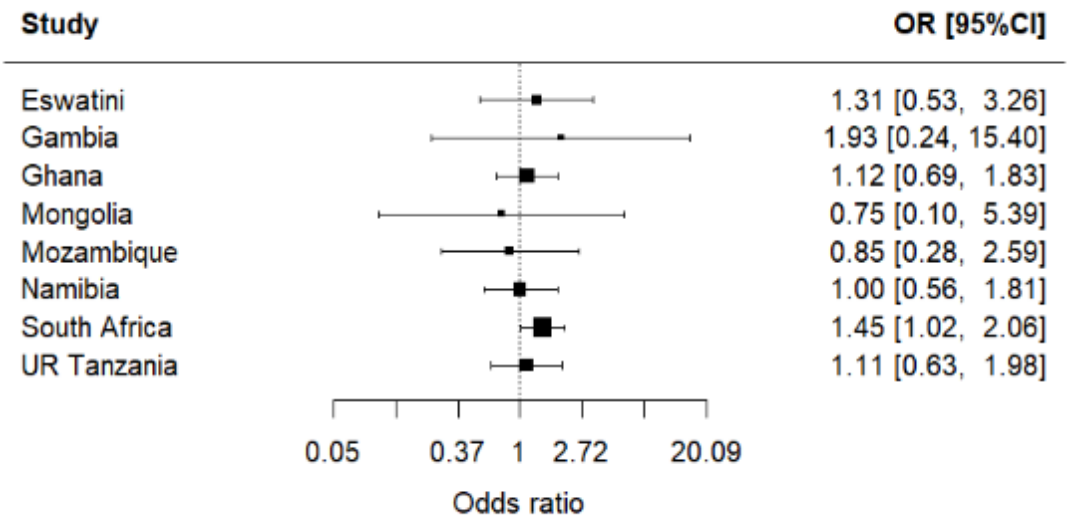
TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
I-squared=35.4%, p=0.15, tau2=0.01
Estimates were adjusted for age and gender of participants

Figure 3-3. Current smoking in members of households with TB compared to those without TB, by region



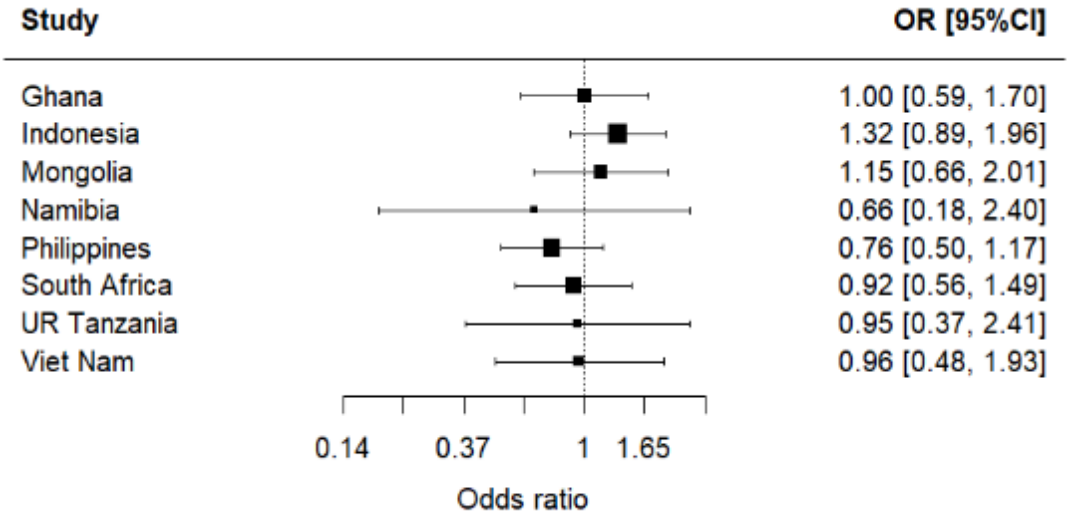
The pooled estimates are based on one-stage meta-analysis.

Figure 3-4.Alcohol drinking twice per week or more in members of households with TB compared to those without TB



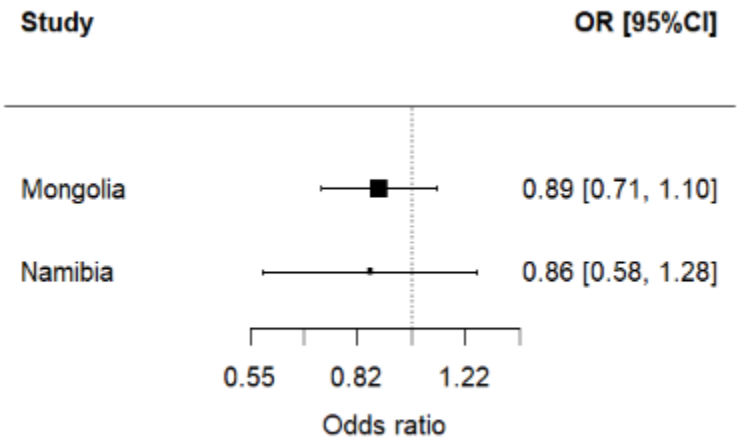
TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
I-squared=0%, p=0.93, tau2=0
Estimates were adjusted for age and gender of participants

Figure 3-5. Diabetes in members of households with TB compared to those without TB



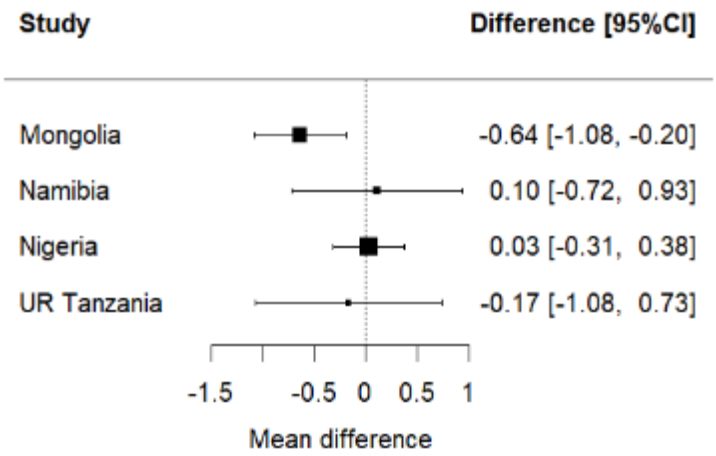
TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
I-squared=0%, p=0.75, tau2=0
Estimates were adjusted for age and gender of participants.

Figure 3-6. Hypertension in members of households with TB compared to those without TB



TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
I-squared=0%, p=0.88, tau2=0.00
Estimates were adjusted for age and gender of participants.

Figure 3-7.BMI in members of households with TB compared to those without TB



TB: tuberculosis; CI: 95% confidence interval; BMI: body mass index
I-squared=50.4%, p=0.11, tau2=0.08
Estimates were adjusted for age and gender of participants

3.4.3. Predictors for NCD and NCD risk factors in members of households

In the models including age and sex of people with TB, household members of current smokers were more likely to be current smokers themselves (aOR 1.46; 95% CI: 1.23-1.74) (Table 3-9).

Table 3-9. Association between NCD or their risk factors in people with TB and those in members of households with TB, adjusted for age and gender of TB patients

	Current smoker	**Alcohol drinking twice per week or more**	**Diabetes**	**Hypertension**	**BMI**
NCD/NCD risk factors in people with TB in the same households	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**Difference in Kg/m^2 (95% CI)**
Current smoker	1.47 (1.23-1.76), p < 0.0001				
Alcohol drinking twice per week or more	-	1.45 (0.62-3.39), p = 0.3922	-	-	-
Diabetes	-	-	0.19 (0.00-77.81), p = 0.5782	-	-
Hypertension	-	-	-	1.31 (0.84-2.06), p = 0.2385	-
BMI per 1 kg/m^2 increase	-	-	-	-	0.08 (0.01-0.16), p = 0.0358

Note: Odds ratios were adjusted for age and gender of TB patients in the same households. Age and BMI were included in the model as continuous variables.
E.g. OR for age per 10-year increase indicates an increase in odds for each 10-year increase in age.
OR: odds ratio; CI: confidence interval; BMI: body mass index

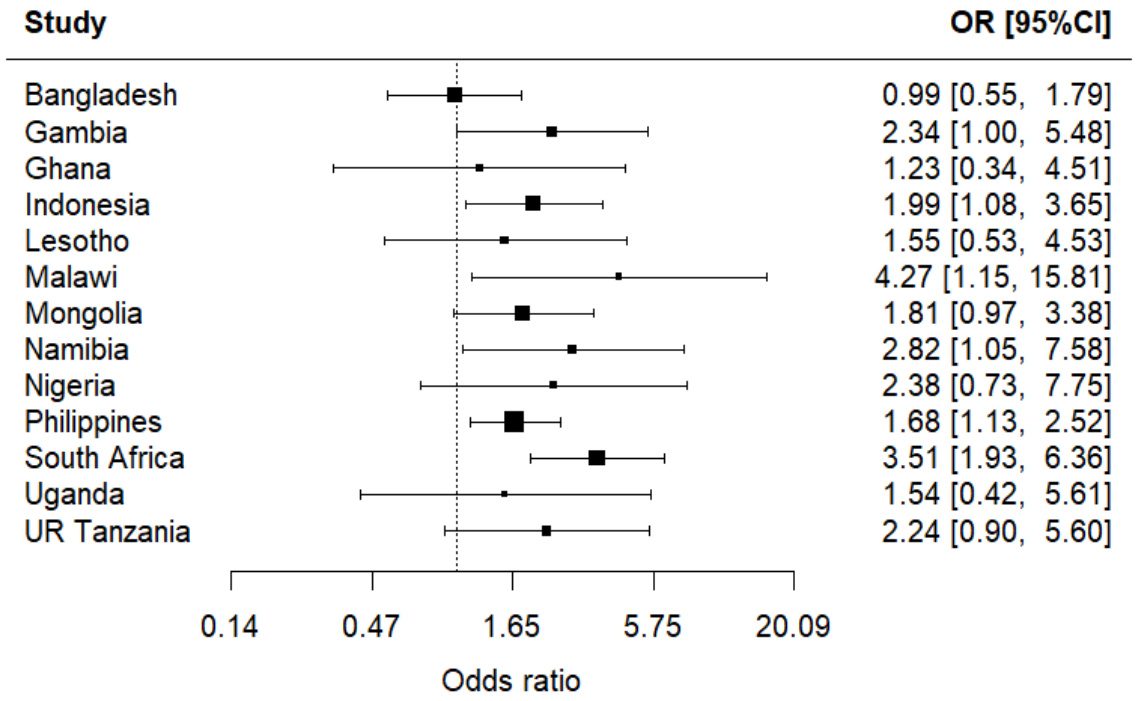
When age and gender of the household members were added to the models, male (aOR 7.09; 95% CI 4.00-12.56) and older age (aOR per 10-year increase 1.08; 95% CI 1.03- 1.13) were associated with being current smokers (Table 3-10). Current smoking of people with TB remained associated with their household members being current smokers (aOR 1.70; 95% CI 1.36- 2.11). The proportion of variability due to between-study heterogeneity was small (I-squared = 0%, p = 0.54, tau^2 = 0.04), with aOR ranging from 0.99 to 4.27 (Figure 3-9).

Table 3-10. Association between NCD or their risk factors in people with TB and those in members of households with TB, adjusted for age and gender of TB patients and household members

	Current smoker	**Alcohol drinking twice per week or more**	**Diabetes**	**Hypertension**	**BMI**
NCD/NCD risk factors in people with TB in the same households	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**Difference (95% CI) kg/m^2**
Current smoker	1.74 (1.37- 2.21), p < 0.0001	-	-	-	-
Alcohol drinking twice per week or more	-	1.55 (0.53-4.52), p = 0.4254	-	-	-
Diabetes	-	-	0.14 (0.00-763.70), p = 0.6478	-	-
Hypertension	-	-	-	1.31 (0.80-2.17), p = 0.2865	-
BMI per 1 kg/m^2 increase	-	-	-	-	0.08 (0.01-0.16), p = 0.0292

Note: Odds ratios were adjusted for age and gender of both TB patients and their household members. Age and BMI were included in the model as continuous variables. E.g. OR for age per 10-year increase indicates an increase in odds for each 10-year increase in age. OR: odds ratio; CI: confidence interval; BMI: body mass index

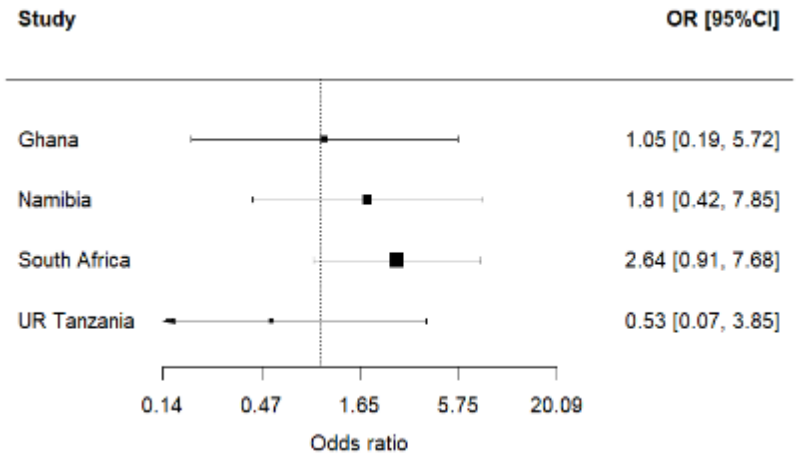
Figure 3-8.Association between current smoking of people with TB and the same in their household members



TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
Note: Estimates were adjusted for age and gender of both people with TB and household members themselves
Eswatini and Mozambique are not presented due to extremely wide CI, ranging from 0 to > 100000.
I-squared=0% (95% CI 0-53.6), p=0.54, tau2=0.04

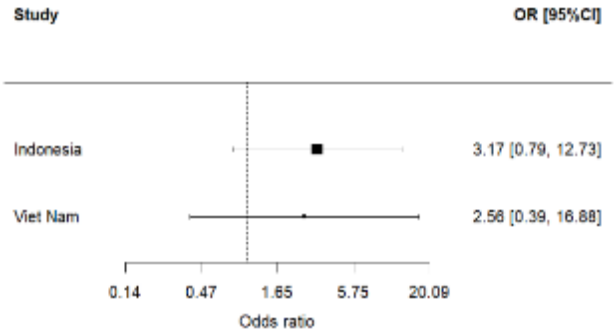
For alcohol drinking (≥ twice per week vs less), hypertension and diabetes, the same conditions in people with TB did not significantly predict their presence in the household members (Table 3-10 and Figures 3-10, 3-11, and 3-12). A higher BMI in people with TB in the same households was associated with higher BMI in household members (Difference per 1kg/m^2 increase in BMI; 0.09 95% CI 0.02-0.16), but the level of the increase was small. The proportion of variability due to between-study heterogeneity was small because of the large confidence intervals within studies (I-squared=0%, p=0.43, tau^2=0.00, Figure 3-13).

Figure 3-9. Association between alcohol drinking of people with TB and the same in their household members



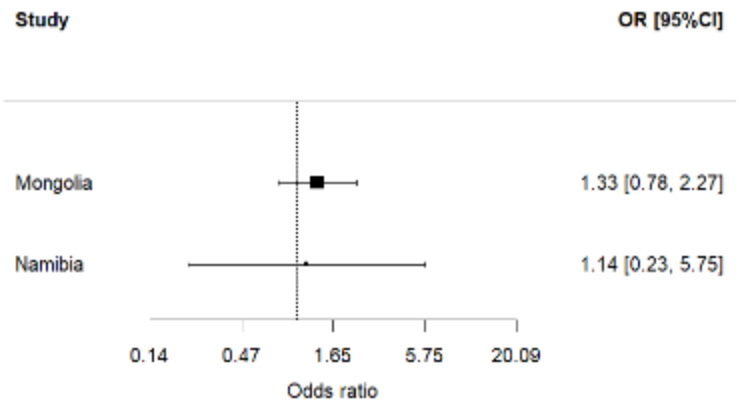
TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
Note: Estimates were adjusted for age and gender of both people with TB and household members themselves
Studies are not presented in the plot when the model failed to converge or standard errors were extremely large resulting in confidence intervals ranging from zero to infinity.
I-squared=0% (95% CI 0-79.2), p=0.68, tau2=0

Figure 3-10. Association between diabetes of people with TB and the same in their household members



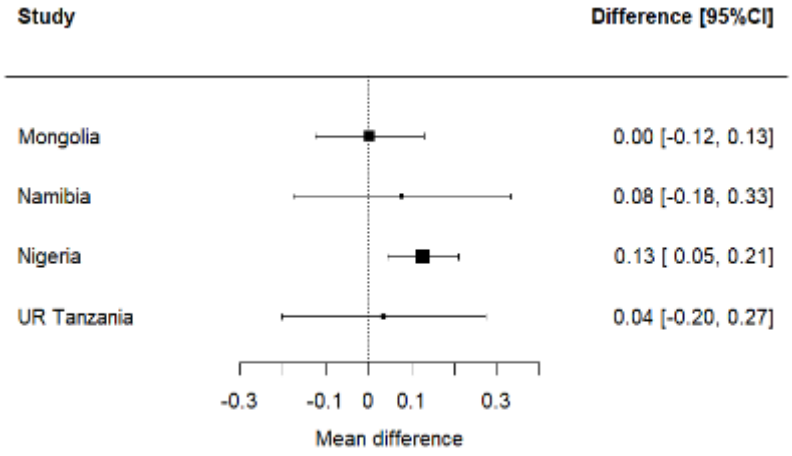
TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
Note: Estimates were adjusted for age and gender of both people with TB and household members themselves
Studies are not presented in the plot when the model failed to converge or standard errors were extremely large resulting in confidence intervals ranging from zero to infinity.
I-squared=0% (95% CI 0-67.6), p=1, tau2=0

Figure 3-11. Association between hypertension of people with TB and the same in their household members



TB: tuberculosis; OR: odds ratio; CI: 95% confidence interval
Note: Estimates were adjusted for age and gender of both people with TB and household members themselves
Only two studies reported data on hypertension; hence, between-study heterogeneity was not estimatable.

Figure 3-12. Association between BMI of people with TB and the same in their household members



TB: tuberculosis; BMI: body mass index; CI: 95% confidence interval
Note: Estimates were adjusted for age and gender of both people with TB and household members themselves.
I-squared=0% (95% CI 0-84.7), p=0.43, tau2=0

3.4.4. Sensitivity analysis

When alcohol drinking was dichotomised into any drinking vs no drinking (Table 3-11), members of households with TB were significantly more likely to drink alcohol (aOR 1.19, 95% CI 1.06-1.33), while the point estimate did not differ from the primary analysis.

Table 3-11.Sensitivity analysis- the association between any alcohol drinking and household status

	Unadjusted model		Adjusted for age and gender	
Group	OR (95% CI)	P value	OR (95% CI)	P value
Member of households without TB	1	-		
Members of households with TB	1.15 (1.03-1.29)	0.0128	1.19 (1.06-1.33)	0.0036

OR: odds ratio; CI: confidence interval; TB: tuberculosis

When excluding six countries that collected NCD data only in a subset of participants, the findings for smoking did not differ significantly (for current smoking in members of households with TB: aOR 1.32 (95% CI 1.22- 1.43), $p < 0.0001$) (Tables 3-12, 3-13, and 3-14). Alcohol drinking was significantly more common in members of households with TB (aOR 1.44, 95% CI 1.02-2.03) (Table 3-12).

Table 3-12.Sensitivity analysis- prevalence of NCD/NCD risk factors in members of households with TB compared to those without TB

	Current smoker	**Alcohol drinking twice per week or more**	**Diabetes**	**Hypertension**	**BMI**
Group	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	Difference in Kg/m^2 (95% CI)
Member of households without TB	1	1	1	1	-
Members of households with TB (adjusted for age and gender)	1.32 (1.22- 1.43), $p < 0.0001$	1.44 (1.02-2.03), $p = 0.0392$	1.00 (0.80-1.25), $p = 0.9935$	0.89 (0.71-1.10), $p = 0.2669$	-0.15 (-0.43; 0.12), $p = 0.2758$

Note: Excluding surveys that collected NCD/NCD risk factors only in a subset of participants. Odds ratios were adjusted for age and gender.
NCD: non-communicable diseases; OR: odds ratio; CI: confidence interval; BMI: body mass index

Table 3-13.Sensitivity analysis- Association between NCD or their risk factors in people with TB and those in members of households with TB, adjusted for age and gender of TB patients

	Current smoker	**Alcohol drinking twice per week or more**	**Diabetes**	**Hypertension**	**BMI**
NCD/NCD risk factors in people with TB in the same households	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**Difference in Kg/m^2 (95% CI)**
Current smoker	1.52 (1.27-1.83), p < 0.0001				
Alcohol drinking twice per week or more	-	7.01 (0.39-127.38), p = 0.1879	-	-	-
Diabetes	-	-	0.15 (0.00-1078.56), p = 0.6676	-	-
Hypertension	-	-	-	1.32 (0.82-2.13), p = 0.2562	-
BMI per 1 kg/m^2 increase	-	-	-	-	0.10 (0.02-0.18), p = 0.0102

Note: Odds ratios were adjusted for age and gender of TB patients in the same households. Age and BMI were included in the model as continuous variables.
NCD: non-communicable diseases; OR: odds ratio; CI: confidence interval; BMI: body mass index

Table 3-14.Sensitivity analysis- Association between NCD or their risk factors in people with TB and those in members of households with TB, adjusted for age and gender of TB patients and household members

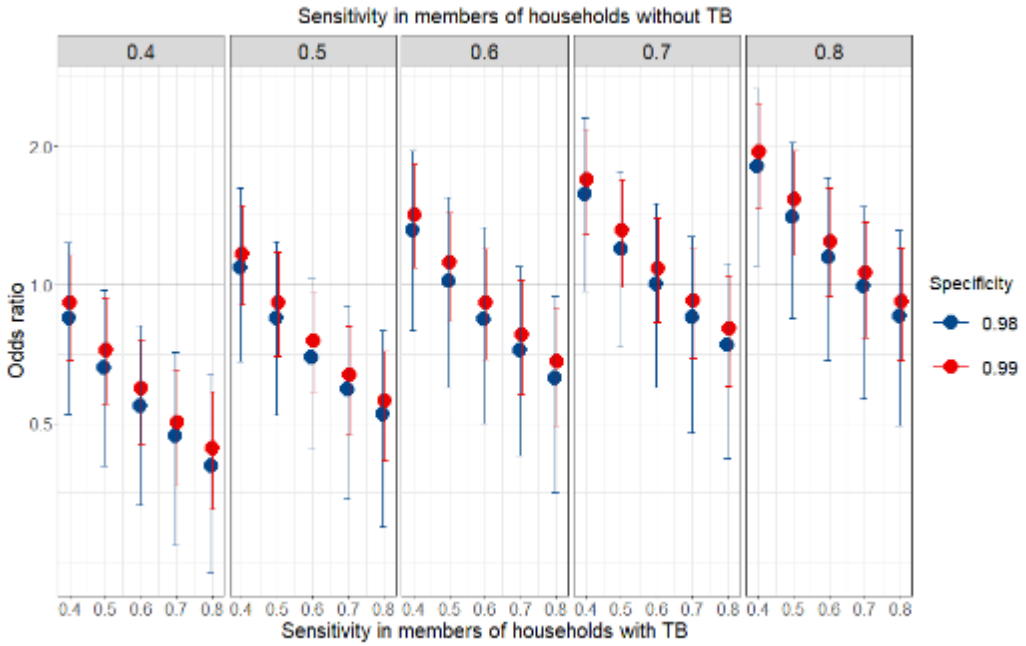
	Current smoker	**Alcohol drinking twice per week or more**	**Diabetes**	**Hypertension**	**BMI**
NCD/NCD risk factors in people with TB in the same households	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95%CI)**	**Difference (95% CI) kg/m^2**
Current smoker	1.92 (1.54- 2.41), p < 0.0001	-	-	-	-
Alcohol drinking twice per week or more	-	5.72 (0.25-129.26), p = 0.2724	-	-	-
Diabetes	-	-	0.39 (0.00-384.75), p = 0.789	-	-
Hypertension	-	-	-	1.40 (0.80-2.46)	-
BMI per 1 kg/m^2 increase	-	-	-	-	0.10 (0.02- 0.18)

Note: Odds ratios were adjusted for age and gender of both TB patients and their household members. Age and BMI were included in the model as continuous variables. E.g. OR for age per 10-year increase indicates an increase in odds for each 10-year increase in age
NCD: non-communicable diseases; OR: odds ratio; CI: confidence interval; BMI: body mass index

Figures 3-14 and 3-15 present the sensitivity analysis exploring the impact of the misclassification of diabetes and hypertension. For the presence of diabetes in household members with TB, the uncertainty intervals were wide and the direction of the association was driven by the direction and the extent of differential misclassification of diabetes status (Figure 3-14). Similarly, the association between hypertension and being members of households with TB depends significantly on the accuracy of self-reported hypertension (Figure 3-15). These findings suggest that the

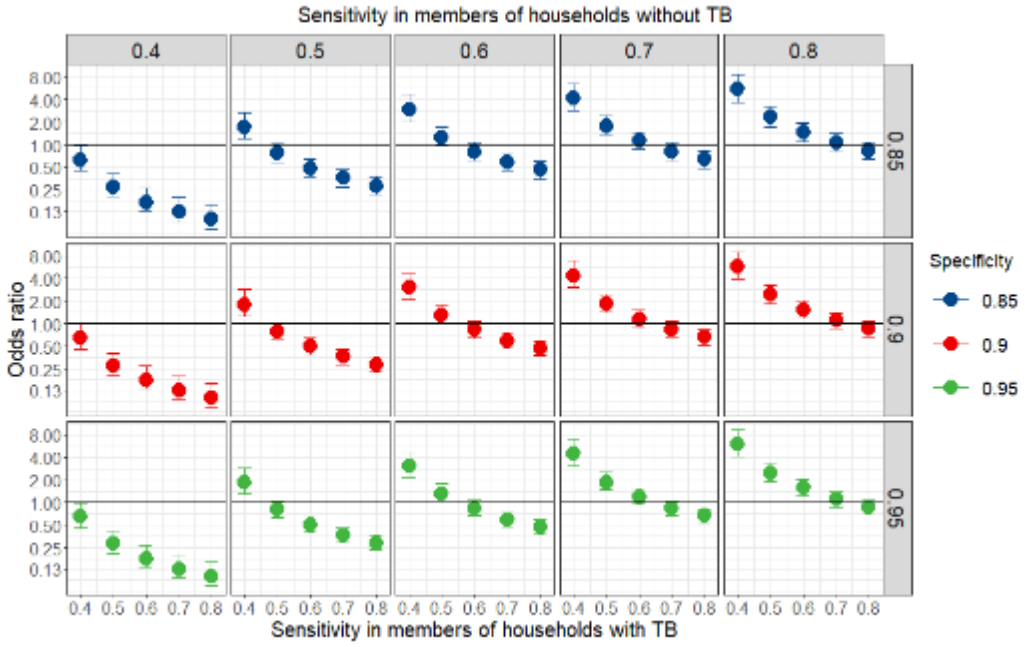
true association remains inconclusive due to the potential misclassification of self-reported diabetes and hypertension.

Figure 3-13.Sensitivity analysis-impact of misclassification of diabetes on its association with members of households with TB



Odds ratios are adjusted for age and gender.
Odds ratios in the analysis using original diabetic status: OR 0.95 (95% CI 0.78-1.17)
The figure presents how the true association between diabetes and being a member of households with TB changes depending on the accuracy of self-reported diabetes. The uncertainty intervals are wide and mostly overlap with null. The direction of the association is driven by the direct and the extent of differential misclassification.

Figure 3-14.Sensitivity analysis-impact of misclassification of hypertension on its association with members of households with TB



Odds ratios are adjusted for age and gender.
Odds ratios in the analysis using original hypertension status: 0.88 (0.74-1.06)
The figure presents how the true association between hypertension and being a member of households with TB changes depending on the accuracy of the hypertension status in surveys. Overall, when the sensitivity and specificity of hypertension are the same between members of households with TB and those without TB (i.e. non-differential misclassification), the odds are close to null, with uncertainty intervals overlapping with one. The direction of the true association heavily depends on the direction and the magnitude of the differential misclassification.

3.5. Discussion

This study drew from large nationally representative surveys in African and Asian countries with high TB incidence. It highlights that the prevalence of smoking is slightly higher among individuals living in households with TB (aOR=1.23, 95% CI 1.11-1.38). Notably, participants were more likely to be current smokers if they resided with people with TB-affected individuals who also smoked. This is the first study, to my knowledge, examining smoking clustering in households with TB patients. Such clustering, including of other conditions, might elevate the TB risk for household contacts.

The model used in this study was not designed to establish causal relationships and included only age and gender as covariates. The observed higher smoking rates among household members of TB patients may be indicative of shared lifestyle or socioeconomic factors. Previous research has shown smoking concordance among

spouses.[172,173] However, since my model adjusted only age and gender, other influencing factors likely played a role. Regardless of the underlying reasons, the increased smoking prevalence in TB-affected households underlines the need to address smoking, a critical shared risk factor for both TB and NCDs.

For alcohol use, the primary analysis did not show a significant association with being a member of a TB-affected household. However, sensitivity analyses, which varied the definition of alcohol use and excluded six countries, indicated a possible increase in the prevalence of alcohol consumption among these household members. Due to these inconsistent findings, the association remains unclear. The significant amount of missing data on alcohol consumption might have affected statistical power, even after imputation. Furthermore, the categorisation of alcohol use was challenging due to variations in data collection methods.

Diabetes and hypertension prevalence in households with TB members did not significantly differ from those in non-TB households. However, these figures are likely underestimates, as they were based predominantly on self-reported data. Sensitivity analyses suggest that the true associations remain uncertain due to potential under-detection. The national diabetes prevalence in surveyed countries ranges from 6% to 13%,[144] but my study found prevalence rates between 2.4 to 5.1%, indicating that household members of people with TB may not be aware of their diabetes. Screening for diabetes in these contacts, alongside TB preventive treatment, could be a reasonable strategy, potentially reducing their TB risk. [174]

This study's strength lies in its use of data from 16 countries with high TB burden across Africa and Asia. While not all surveys provided data for every outcome, each analysis included a substantial number of nationally representative participants. A major limitation is the reliance on self-reported data for ascertaining NCDs like diabetes and hypertension, likely leading to underestimation of NCD burden and potential bias in associations. Future surveys should incorporate standardized NCD data collection, such as the WHO STEPwise approach, to facilitate robust analysis of the interplay between NCDs and TB. [175] Another limitation is the lack of data on other NCDs, such as dyslipidaemia and chronic kidney disease, highlighting the need for comprehensive studies on NCD prevalence and multimorbidity through systematic screening. Additionally, due to the limited number of surveys for certain

outcomes, my models used fixed slopes; employing random slopes to account for country-specific heterogeneity would have been more suitable.

Lastly, as of July 1, 2024, a new prevalence survey in India has been completed. I did not include data from the new survey. Furthermore, aggregated data that could be used in the meta-analysis were lacking. Moreover, data collection for my IPD stopped in January 2022 to allow sufficient time for, obtaining necessary data sharing agreements (which took ~12 months), data harmonisation and data analysis. Sharing anonymised data from prevalence surveys in a public repository to facilitate further research without administrative burdens should be encouraged. The large sample size of the survey in India (N=354,541) could influence the results of the present analysis,[176] and its impact is difficult to predict without specific data. However, the concordance of smoking habits within households has been reported.[177]

3.6. Conclusion

TB prevalence survey data reveal that self-reported diabetes prevalence is lower than national estimates, pointing to underdiagnosis. The absence of data on other NCDs represents a missed opportunity to obtain valuable insights from TB prevalence surveys. Conversely, the study suggests a higher smoking frequency in TB-affected households, particularly when a person with TB in the same household is a smoker. Given the smoking clustering observed in these households, targeted household-level interventions addressing smoking could simultaneously reduce NCD and TB risks. A well-designed prospective study with systematic NCD screening among TB contacts is necessary to accurately assess the burden of NCDs and their risk factors.

4. Association of NCD and NCD risk factors with subclinical-to-symptomatic spectrum of TB

4.1. Abstract

Background

NCD and NCD risk factors such as smoking increase the risk for TB. However, data are limited on the risk of prevalent TB associated with these factors in the context of population-wide systematic screening. Furthermore, data are lacking on the association between NCDs and NCD risk factors with different manifestations of TB (symptomatic or asymptomatic), where approximately 50% risk being asymptomatic but bacteriologically positive (subclinical). Quantifying the risk of prevalent TB diseases and describing associations with NCD and NCD risk factors can help countries plan screening activities. I conducted an IPD meta-analysis of national and sub-national TB prevalence surveys to synthesise the evidence on the risk of symptomatic and subclinical TB in people with NCDs and/or NCD risk factors.

Methods

In this systematic review and IPD meta-analysis, I identified eligible prevalence surveys in LMIC that reported at least one NCD (e.g. diabetes) or NCD risk factor (e.g. smoking, alcohol use) through the archive maintained by the World Health Organization and by searching in Medline and Embase from 1 January 2000 to 10 August 2021. The search was updated on 23 March 2023. I performed a one-stage meta-analysis using multivariable multinomial models. I estimated the proportion of and the odds ratio for subclinical and symptomatic TB compared to people without TB for current smoking, alcohol use, and self-reported diabetes, adjusted for age and gender. Subclinical TB was defined as microbiologically-confirmed TB without symptoms of current cough, fever, night sweats, or weight loss and symptomatic TB with at least one of these symptoms. I assessed heterogeneity using forest plots and I^2 statistic. Missing variables were imputed through multi-level multiple imputation. This study is registered with PROSPERO (CRD42021272679)

Results

I obtained IPD from 16 national surveys out of 21 national and five sub-national surveys identified (5 in Asia and 11 in Africa, N= 740,815). Across surveys,15.1% to 56.7% of TB were subclinical (median: 38.1%). In the multivariable model, current

smoking was associated with both subclinical (OR 1.67, 95% CI 1.27-2.40) and symptomatic TB (OR 1.49, 95% CI 1.34-1.66). Self-reported diabetes was associated with symptomatic TB (OR 1.67, 95% CI 1.17-2.40) but not with subclinical TB (OR 0.92, 95% CI 0.55-1.55). For alcohol drinking ≥ twice per week vs no alcohol drinking, the estimates were imprecise (OR 1.59, 95% CI 0.70-3.62 for subclinical TB and OR 1.43, 95% CI 0.59-3.46 for symptomatic TB). For the association between current smoking and symptomatic TB, I^2 was high (76.5% (95% CI 62.0-85.4), while the direction of the point estimates was consistent except for three surveys with wide CIs.

Conclusion

The present study suggests that current smokers are more likely to have both symptomatic and subclinical TB. These individuals can be prioritised for intensified screening, such as the use of chest X-rays in the context of community-based screening. People with self-reported diabetes are also more likely to have symptomatic TB, but the association is unclear for subclinical TB. Chest X-rays in people with self-reported diabetes may not find more subclinical TB than the general population.

4.2. Introduction

In 2022, 7.5 million people with TB were reported globally out of an estimated 10.6 million people who developed TB, leaving 3 million people with TB not diagnosed or reported.[1] The WHO recommends systematic screening for active TB disease in specific populations or settings to help find people with TB and fill the gap.[112] Systematic screening intends to identify individuals who have TB disease, either symptomatic or asymptomatic, at the time of screening (i.e. prevalent TB).[112] The target populations include, for example, contacts, people living with HIV, people attending health facilities with clinical risk factors, such as diabetes and smoking, as well as the general population in areas with an estimated TB prevalence of 0.5% or higher. WHO recommends prioritising groups for screening "based on their risk of TB, the risk of poor treatment outcomes if diagnosis is delayed and the size of the risk group in a given setting."[112] Quantifying the risk of prevalent TB in people with different factors allows countries to estimate the yield of systematic screening and help plan the targeted implementation of screening activities.[178] Thus, WHO published a tool to estimate yields of systematic screening using parameters such as the risk ratio for TB associated with specific risk factors. NCD, such as diabetes and NCD risk factors (e.g. smoking and alcohol use), are known to increase the risk for TB. For example, systematic reviews reported a 1.5-3.5-fold risk for developing TB in people with diabetes[12,13] and around 2.5-fold risk for TB disease or TB infection in people who smoke.[179] However, most studies underpinning the recommendations are based on case-control studies, cohort studies assessing incident TB, or studies using TB diagnosed through routine care.[12,13,52,112] Limited data exist on the risk of prevalent TB associated with these factors in the context of systematic screening from countries with a high TB burden.

National TB prevalence surveys are population-based multi-stage cluster sampling surveys whose primary aim is to estimate the national prevalence of TB. Some prevalence surveys collected data on NCD and NCD risk factors such as smoking, alcohol use, and self-reported diabetes. Using IPD from these surveys enables quantifying the risk of prevalent TB by NCDs and NCD risk factors. However, no such IPD meta-analysis of prevalence surveys has been done to date.

A recent meta-analysis of aggregated data from TB prevalence surveys found that 36-80% of people with TB do not have symptoms yet bacteriologically positive, so-called subclinical TB; reliance on symptom-based screening will miss those people with subclinical TB.[142] Because of the unavailability of IPD, the previous meta-analysis could not conduct an analysis to understand whether NCD and NCD risk factors (e.g. smoking) can be used to identify people with different manifestations of TB. Understanding predictors for subclinical TB could help prioritise X-ray-based screening for those who are more likely to have it. In addition, the previous review could not apply the same definition of subclinical and symptomatic TB across surveys.[142]

Therefore, I conducted an IPD meta-analysis of national TB prevalence surveys. First, I aimed to quantify the proportion of subclinical TB using the standardised definition. Second, I investigated the risk of symptomatic and subclinical TB in people with NCD and NCD risk factors compared to those without such factors in the context of population-level systematic screening.

4.3. Method

4.3.1. Design

I conducted a systematic review and IPD meta-analysis following the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement.[180] The protocol of this systematic review has been pre-registered.
(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=272679)
The search strategy, selection of studies, and data collection are described in Chapter 3.3.

4.3.2. Outcome

Prevalent TB disease was defined as survey TB cases, which were confirmed bacteriologically either by culture or Gene Xpert.[143] Subclinical TB was defined as bacteriologically-confirmed TB lacking any of the following symptoms of any duration: current cough, weight loss, fever, or night sweats.[181] Conversely, symptomatic TB was defined by the presence of any of these symptoms.

I and another investigator independently reviewed titles and abstracts to identify potentially eligible studies in duplicate. Both of us reviewed full-text articles of those identified through the first screening. Discrepancies were resolved through discussion.

4.3.3. Quality assessment

The prevalence surveys under consideration were conducted following WHO-recommended methodologies, ensuring participant representativeness through random sampling and adherence to recommended screening and diagnostic procedures. [143] Additionally, as there is no established standard for evaluating the quality of cross-sectional studies that investigate associations between exposures and outcomes, I employed a quality assessment tailored to my specific analysis. This assessment included elements from the Risk Of Bias In Non-randomised Studies - of Exposures (ROBINS-E) tool. [182] In this context, I evaluated the participation rate to assess the risk of selection bias risk and examined the methods used for diagnosing TB and NCDs to determine the risk of bias due to exposure misclassification. Furthermore, I collected details on TB screening and confirmation methods to assess the risk of bias due to outcome misclassification and checked the missingness of exposure and outcome variables.

4.3.4. Statistical analysis

Handling of missing data

I conducted multi-level fully conditional specification for multiple imputation. The imputation model incorporated several variables: TB categorised into three groups (no TB, subclinical TB, and symptomatic TB), various predictors (including diabetes, alcohol use, smoking history, previous TB history, age, and gender), and auxiliary variables (such as TB symptoms and chest X-ray results). Most of these variables, with the exception of age and gender, exhibited sporadic or systematic missing data; thus, they were imputed. To ensure plausible regional HIV prevalence estimations, I also included a binary indicator distinguishing African countries from Asian countries in the model. The model accounted for clustering within surveys. Although I initially planned to account for clustering within households and/or sampling clusters, the

model failed to converge, likely due to minimal within-household variation. Consequently, the model accounted for survey-level clustering alone.

I generated 20 multiply imputed data sets with 20 iterations between successive imputation. Model convergence was assessed visually by examining trace plots. For the primary analyses, these multiply imputed datasets were used, with substantive models applied to each dataset. The results of these models were combined using Rubin's rules.[183]

Descriptive analysis and regression models

I calculated the crude prevalence of TB and the proportion of subclinical TB by country utilizing the imputed datasets. I presented clinical and demographic variables by TB status. My approach involved conducting multi-level logistic regression analyses to calculate the odds ratio for all TB types, combining both symptomatic and subclinical TB. Additionally, I employed multi-level multinomial regression to ascertain the odds ratios for subclinical and symptomatic TB separately, in comparison to individuals without TB. Predictors of interest included current smoking, past smoking, alcohol use, diabetes, age, and gender. It is important to note that the surveys in this study identified diabetes prevalence based on self-reporting rather than blood tests. While self-reported diabetes has limited sensitivity (approximately 50%), its specificity exceeds 95% in diagnosing prevalent diabetes.[184,185] Despite its limitations, I included self-reported diabetes in my analysis to explore its potential in identifying people with higher TB risk, especially in contexts where laboratory testing is difficult to access. Other NCD were not included due to limited data availability. I also included HIV and past history of TB in order to compare the level of risk associated with smoking, alcohol use, and diabetes with risk factors that are recommended for systematic screening.[112] Smoking history was modelled in two ways: as a binary variable differentiating current from non-current smokers (including never and past smokers), and as a categorical variable distinguishing current, past, and never smokers. The binary variable aimed to determine if current smoking status could help identify individuals at a higher risk for TB or specific TB manifestations. The categorical variable was to evaluate if past smoking maintains an association with TB risk compared to never smoking. Both univariable and multivariable models were conducted. In the univariable model, each

risk factor was analysed separately. Subsequently, I conducted multivariable modelling, adding current smoking, past smoking, alcohol use, diabetes, past history of TB, and HIV one at a time, adjusted for age and gender alone. This model intended to examine if these factors can be used to identify individuals who are more likely to have TB overall or TB with specific manifestations and hence can be prioritised for systematic screening, regardless of age and gender. The present analysis did not intend to examine causal associations. The models included random intercepts for surveys and households to account for clustering. I explored the heterogeneity in the adjusted odds ratios between countries through forest plots. I quantified the proportion of total variability due to between-study heterogeneity by calculating I-squared statistics.

As a sub-group analysis, I repeated the above analysis in HIV-negative individuals, given that people living with HIV are already prioritised for systematic screening regardless of the presence of other risk factors.[186] To do this, I excluded HIV-positive participants and participants with unknown HIV status before multiple imputation.

Sensitivity analysis

First, I examined various categorisations of alcohol drinking: 1) any drinking vs no drinking; and 2) drinking ≥ twice per week vs drinking < twice per week.

Second, I repeated the analyses by excluding: 1) Tanzania alone due to a concern about the validity of their bacteriologically positive cases,[187] 2) countries where NCD data were collected only from a subset of the participants, and 3) countries that did not collect all four symptoms.

Third, to examine the impact of systematically and sporadically missing data on alcohol drinking and diabetes, I repeated the analyses by restricting to studies with minimal missing data.

Fourth, to explore the impact of misclassification of self-reported diabetic status, I conducted a record-level quantitative bias analysis assuming different levels of sensitivity and specificity of self-reported diabetes.

I tested both non-differential and differential misclassification of diabetic status by the presence of TB. Based on previous studies, I assumed the sensitivity of self-reported diabetes to be 40% or 50% in people without TB.[147,148] In people with TB, I tested the same levels of sensitivity as in those without TB (i.e. non-differential misclassification) as well as higher levels, ranging from 50% to 80%. This quantitative analysis allowed me to examine if a higher likelihood of diabetes being diagnosed in people with TB than in those without TB can lead to spurious associations between self-reported diabetes and TB. Given that the prevalence of self-reported diabetes was 2.8% among participants without TB, the specificity in this population is inferred to be at least 97.2%, in line with existing literature.[147,148] Hence, I tested 98% and 99% specificity. I adapted the approach described by Fox et al. while using fixed levels of sensitivity and specificity.[146] I first sampled one of the 20 multiply imputed datasets and estimated positive and negative predictive values for diabetes given the observed diabetic status. Second, using the predictive values, I simulated a new variable representing true diabetic status drawing at random from a Bernoulli distribution. A multinomial regression model was then fitted with this new variable, adjusted for age and gender. To incorporate random errors, I repeatedly simulated this process 1000 times, each time adding a standard normal deviate, scaled by the bias-adjusted association's standard error, to the point estimate. The resulting median and 2.5th and 97.5th percentiles were reported as uncertainty intervals. I repeated the above process 1000 times and presented the median and 2.5th and 97.5th percentiles as uncertainty intervals. For computational efficiency, the multinomial model excluded random intercepts for households. Finally, I compared these findings to those derived from models using reported diabetic status.

4.3.5. Ethics

This IPD meta-analysis was approved by the UCL Research Ethics Committee (18969/001). All participants provided informed consent to participate in the primary surveys included in this meta-analysis.

4.4. Results

4.4.1. Characteristics of included studies

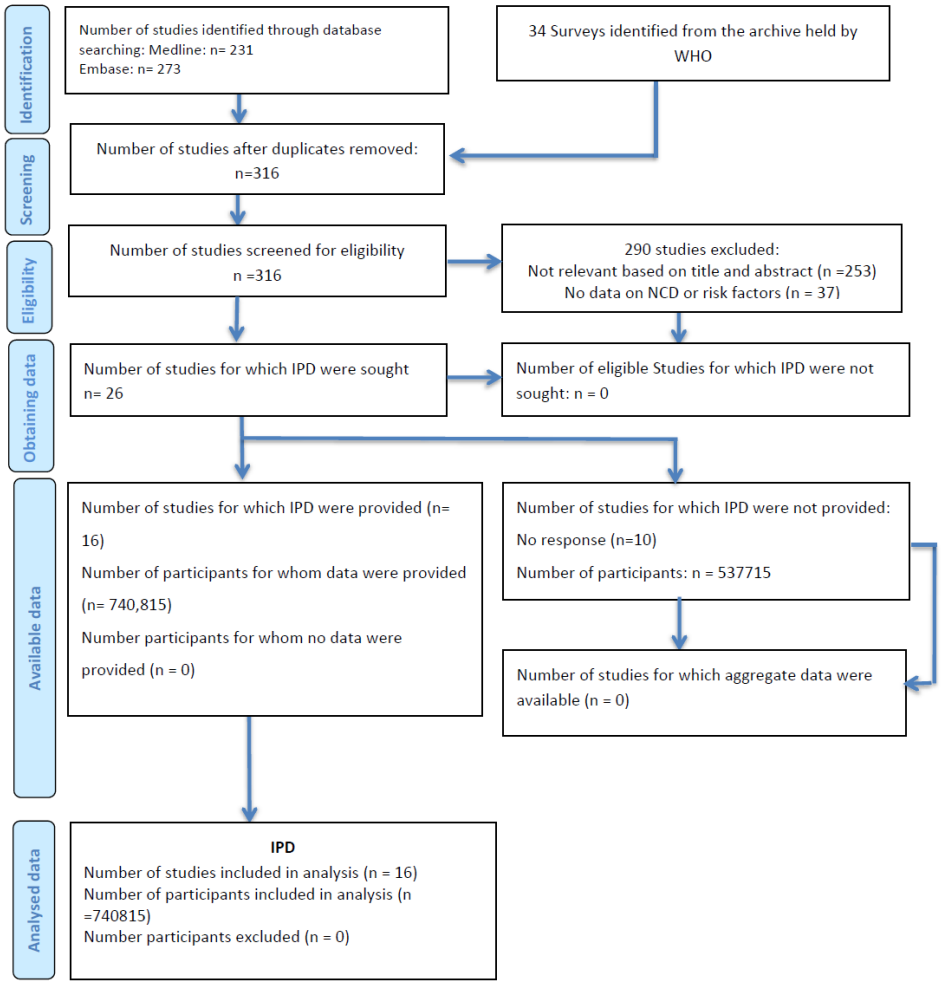
In the archive of TB prevalence surveys held by WHO, 21 surveys were found to be eligible (Figure 4-1). Sixteen (73%) agreed to share datasets and were included in

the meta-analysis (740,815 participants in total).[151-166] Five surveys (in the Democratic People's Republic of Korea, Ethiopia, Myanmar, Rwanda, and Zimbabwe) did not respond to my request. All of them had data on smoking, two on diabetes, and two on alcohol use. When stratified by the availability of NCD-related variables, for smoking, diabetes, and alcohol use, I included 16 out of 22 eligible national surveys, nine out of 11, and eight out of 10, respectively. The database searches identified five additional eligible studies from Ethiopia,[167] India,[168] Viet Nam,[170] and South Africa and Zambia[171]; however, none of the studies responded to my request before the closure of data collection. All of them were subnational surveys comprising a total of 286,340 participants; each collected data on smoking only as an NCD risk factor.

My meta-analysis included 16 national TB prevalence surveys conducted between 2012 and 2020, including 5 in Asia and 11 in Africa (Table 4-1). In all surveys, there were fewer male participants than females; the proportion of male participants ranged from 39.6 to 46.6%. Of TB cases diagnosed, 3.0% to 11.4% were on treatment. All surveys included individuals aged 15 years or older.

Thirteen studies used sputum smear and culture with or without Xpert MTB/RIF to diagnose TB among participants with TB-suggestive symptoms and/or chest X-ray findings, while the rest[157,160,164] used culture and Xpert MTB/RIF or Xpert MTB/RIF Ultra without smear (Table 4-2).

Figure 4-1.Selection of surveys



IPD: individual participant data; WHO: World Health Organization; NCDs: non-communicable diseases

Table 4-1. Characteristics of included surveys

	Mozambique	Namibia	Nigeria	Philippines	South Africa	United Republic of Tanzania	Uganda	Viet Nam
Year	2017	2017	2012	2016	2017-2019	2012	2014-2015	2017
n	32445	29495	12999	46689	35191	50447	41154	61763
Age (mean (SD))	33.90 (16.70)	37.77 (17.60)	39.19 (17.68)	39.47 (17.62)	40.55 (18.33)	38.14 (17.84)	33.50 (15.76)	46.55 (16.96)
Gender (%)								
Female	18444 (56.8)	16900 (57.3)	7631 (58.7)	25796 (55.3)	21803 (62.0)	29701 (58.9)	23669 (57.5)	34613 (56.0)
Male	14001 (43.2)	12595 (42.7)	5368 (41.3)	20893 (44.7)	13388 (38.0)	20735 (41.1)	17485 (42.5)	27150 (44.0)
NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.0)	0 (0.0)	0 (0.0)
TB (%)								
No	29608 (91.3)	27802 (94.3)	12467 (95.9)	43867 (94.0)	33466 (95.1)	49326 (97.8)	40691 (98.9)	61108 (98.9)
Yes	89 (0.3)	119 (0.4)	66 (0.5)	466 (1.0)	234 (0.7)	159 (0.3)	160 (0.4)	221 (0.4)
NA	2748 (8.5)	1574 (5.3)	466 (3.6)	2356 (5.0)	1491 (4.2)	962 (1.9)	303 (0.7)	434 (0.7)
Diabetes (%)								
No	0 (0.0)	11714 (39.7)	0 (0.0)	44823 (96.0)	32867 (93.4)	5929 (11.8)	0 (0.0)	4154 (6.7)
Yes	0 (0.0)	183 (0.6)	0 (0.0)	1866 (4.0)	1784 (5.1)	61 (0.1)	0 (0.0)	376 (0.6)
NA	32445 (100.0)	17598 (59.7)	12999 (100.0)	0 (0.0)	540 (1.5)	44457 (88.1)	41154 (100.0)	57233 (92.7)
HIV (%)								
Negative	19879 (61.3)	21053 (71.4)	0 (0.0)	0 (0.0)	21800 (61.9)	5695 (11.3)	3972 (9.7)	0 (0.0)
Positive	2966 (9.1)	3338 (11.3)	0 (0.0)	0 (0.0)	4606 (13.1)	307 (0.6)	422 (1.0)	0 (0.0)
NA	9600 (29.6)	5104 (17.3)	12999 (100.0)	46689 (100.0)	8785 (25.0)	44445 (88.1)	36760 (89.3)	61763 (100.0)
Alcohol use (%)								
None	10248 (31.6)	7086 (24.0)	0 (0.0)	0 (0.0)	23323 (66.3)	3744 (7.4)	0 (0.0)	0 (0.0)
Once a week or less	1938 (6.0)	2028 (6.9)	0 (0.0)	0 (0.0)	9858 (28.0)	1166 (2.3)	0 (0.0)	0 (0.0)
Twice a week or more	362 (1.1)	1399 (4.7)	0 (0.0)	0 (0.0)	2010 (5.7)	1085 (2.2)	0 (0.0)	0 (0.0)
NA	19897 (61.3)	18982 (64.4)	44186 (100.0)	46689 (100.0)	0 (0.0)	44452 (88.1)	41154 (100.0)	61763 (100.0)
Smoking (%)								
Never	0 (0.0)	0 (0.0)	39950 (90.4)	28128 (60.2)	0 (0.0)	4640 (9.2)	35412 (86.0)	2453 (4.0)

Past smoking	0 (0.0)	0 (0.0)	2096 (4.7)	7637 (16.4)	0 (0.0)	476 (0.9)	2715 (6.6)	620 (1.0)
Current smoking	1337 (4.1)	2196 (7.4)	2139 (4.8)	10749 (23.0)	9367 (26.6)	875 (1.7)	3020 (7.3)	1459 (2.4)
Non-current smoker (no data on past smoking)	11183 (34.5)	9916 (33.6)	0 (0.0)	0 (0.0)	25750 (73.2)	11 (0.0)	0 (0.0)	0 (0.0)
NA	19925 (61.4)	17383 (58.9)	1 (0.0)	175 (0.4)	74 (0.2)	44445 (88.1)	7 (0.0)	57231 (92.7)
Any TB symptoms (%)								
No	24072 (74.2)	21072 (71.4)	0 (0.0)	25608 (54.8)	29589 (84.1)	0 (0.0)	27941 (67.9)	1329 (2.2)
Yes	7394 (22.8)	8422 (28.6)	3928 (30.2)	19943 (42.7)	5168 (14.7)	1497 (3.0)	13213 (32.1)	11402 (18.5)
NA	979 (3.0)	1 (0.0)	9071 (69.8)	1138 (2.4)	434 (1.2)	48950 (97.0)	0 (0.0)	49032 (79.4)
Past history of TB (%)								
No	31298 (96.5)	26515 (89.9)	12815 (98.6)	43993 (94.2)	32099 (91.2)	49192 (97.5)	40342 (98.0)	60371 (97.7)
Yes	1064 (3.3)	2979 (10.1)	184 (1.4)	2615 (5.6)	2964 (8.4)	740 (1.5)	812 (2.0)	1130 (1.8)
NA	83 (0.3)	1 (0.0)	0 (0.0)	81 (0.2)	128 (0.4)	515 (1.0)	0 (0.0)	262 (0.4)

TB: tuberculosis; SD: standard deviation; HIV: human immunodeficiency virus

	Mozambique	Namibia	Nigeria	Philippines	South Africa	United Republic of Tanzania	Uganda	Viet Nam
Year	2017	2017	2012	2016	2017-2019	2012	2014-2015	2017
n	32445	29495	12999	46689	35191	50447	41154	61763
Age (mean (SD))	33.90 (16.70)	37.77 (17.60)	39.19 (17.68)	39.47 (17.62)	40.55 (18.33)	38.14 (17.84)	33.50 (15.76)	46.55 (16.96)
Gender (%)								
Female	18444 (56.8)	16900 (57.3)	7631 (58.7)	25796 (55.3)	21803 (62.0)	29701 (58.9)	23669 (57.5)	34613 (56.0)
Male	14001 (43.2)	12595 (42.7)	5368 (41.3)	20893 (44.7)	13388 (38.0)	20735 (41.1)	17485 (42.5)	27150 (44.0)
NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.0)	0 (0.0)	0 (0.0)
TB (%)								
No	29608 (91.3)	27802 (94.3)	12467 (95.9)	43867 (94.0)	33466 (95.1)	49326 (97.8)	40691 (98.9)	61108 (98.9)
Yes	89 (0.3)	119 (0.4)	66 (0.5)	466 (1.0)	234 (0.7)	159 (0.3)	160 (0.4)	221 (0.4)
NA	2748 (8.5)	1574 (5.3)	466 (3.6)	2356 (5.0)	1491 (4.2)	962 (1.9)	303 (0.7)	434 (0.7)
Diabetes (%)								
No	0 (0.0)	11714 (39.7)	0 (0.0)	44823 (96.0)	32867 (93.4)	5929 (11.8)	0 (0.0)	4154 (6.7)

Yes	0 (0.0)	183 (0.6)	0 (0.0)	1866 (4.0)	1784 (5.1)	61 (0.1)	0 (0.0)	376 (0.6)
NA	32445 (100.0)	17598 (59.7)	12999 (100.0)	0 (0.0)	540 (1.5)	44457 (88.1)	41154 (100.0)	57233 (92.7)
HIV (%)								
Negative	19879 (61.3)	21053 (71.4)	0 (0.0)	0 (0.0)	21800 (61.9)	5695 (11.3)	3972 (9.7)	0 (0.0)
Positive	2966 (9.1)	3338 (11.3)	0 (0.0)	0 (0.0)	4606 (13.1)	307 (0.6)	422 (1.0)	0 (0.0)
NA	9600 (29.6)	5104 (17.3)	12999 (100.0)	46689 (100.0)	8785 (25.0)	44445 (88.1)	36760 (89.3)	61763 (100.0)
Alcohol use (%)								
None	10248 (31.6)	7086 (24.0)	0 (0.0)	0 (0.0)	23323 (66.3)	3744 (7.4)	0 (0.0)	0 (0.0)
Once a week or less	1938 (6.0)	2028 (6.9)	0 (0.0)	0 (0.0)	9858 (28.0)	1166 (2.3)	0 (0.0)	0 (0.0)
Twice a week or more	362 (1.1)	1399 (4.7)	0 (0.0)	0 (0.0)	2010 (5.7)	1085 (2.2)	0 (0.0)	0 (0.0)
NA	19897 (61.3)	18982 (64.4)	44186 (100.0)	46689 (100.0)	0 (0.0)	44452 (88.1)	41154 (100.0)	61763 (100.0)
Smoking (%)								
Never	0 (0.0)	0 (0.0)	39950 (90.4)	28128 (60.2)	0 (0.0)	4640 (9.2)	35412 (86.0)	2453 (4.0)
Past smoking	0 (0.0)	0 (0.0)	2096 (4.7)	7637 (16.4)	0 (0.0)	476 (0.9)	2715 (6.6)	620 (1.0)
Current smoking	1337 (4.1)	2196 (7.4)	2139 (4.8)	10749 (23.0)	9367 (26.6)	875 (1.7)	3020 (7.3)	1459 (2.4)
Non-current smoker (no data on past smoking)	11183 (34.5)	9916 (33.6)	0 (0.0)	0 (0.0)	25750 (73.2)	11 (0.0)	0 (0.0)	0 (0.0)
NA	19925 (61.4)	17383 (58.9)	1 (0.0)	175 (0.4)	74 (0.2)	44445 (88.1)	7 (0.0)	57231 (92.7)
Any TB symptoms (%)								
No	24072 (74.2)	21072 (71.4)	0 (0.0)	25608 (54.8)	29589 (84.1)	0 (0.0)	27941 (67.9)	1329 (2.2)
Yes	7394 (22.8)	8422 (28.6)	3928 (30.2)	19943 (42.7)	5168 (14.7)	1497 (3.0)	13213 (32.1)	11402 (18.5)
NA	979 (3.0)	1 (0.0)	9071 (69.8)	1138 (2.4)	434 (1.2)	48950 (97.0)	0 (0.0)	49032 (79.4)
Past history of TB (%)								
No	31298 (96.5)	26515 (89.9)	12815 (98.6)	43993 (94.2)	32099 (91.2)	49192 (97.5)	40342 (98.0)	60371 (97.7)
Yes	1064 (3.3)	2979 (10.1)	184 (1.4)	2615 (5.6)	2964 (8.4)	740 (1.5)	812 (2.0)	1130 (1.8)
NA	83 (0.3)	1 (0.0)	0 (0.0)	81 (0.2)	128 (0.4)	515 (1.0)	0 (0.0)	262 (0.4)

TB: tuberculosis; SD: standard deviation; HIV: human immunodeficiency virus

Table 4-2. Quality of individual surveys

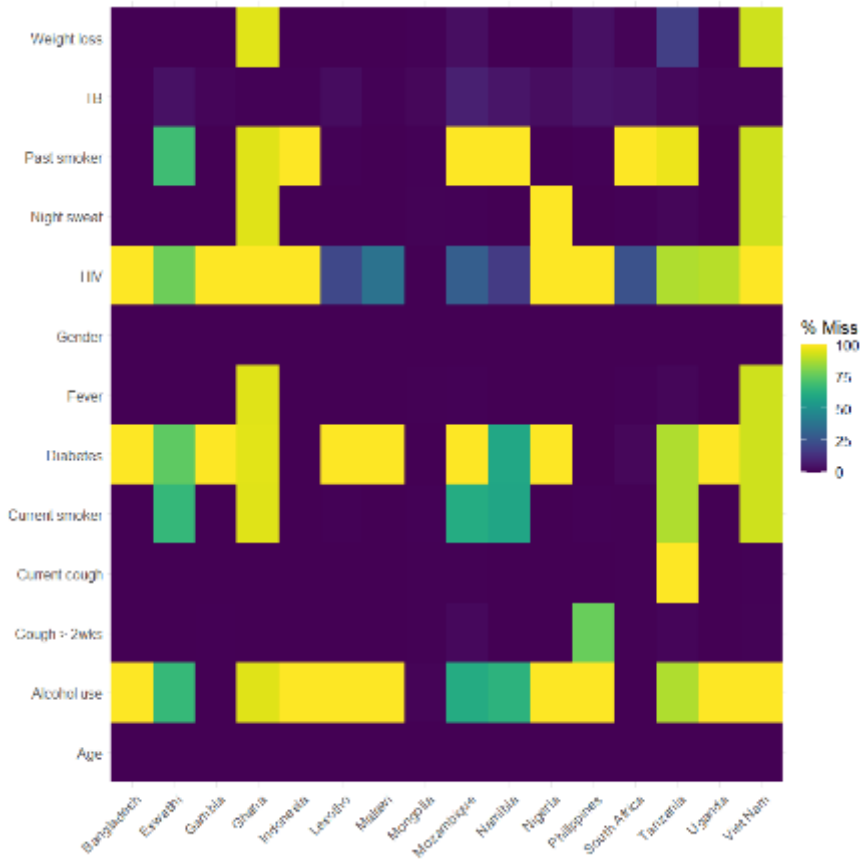
Survey	Selection	Measurement of the outcome			Measurement of the exposure	Missing data	
	# participated/# eligible (%)	Symptom screening criteria	Chest x-ray criteria	Diagnostic method	Diagnosis of diabetes	All four symptoms collected?****	NCDs data sought in all participants?
Bangladesh	98710/108834 (90.7)	Scoring based on cough, haemoptysis, weight loss, fever, and/or night sweats	Any lung abnormality	Smear, culture, and Xpert	NA	Yes	Yes
Eswatini	24358/NA (NA)	Cough of any duration, fever for ≥ 2 weeks, unexplained weight loss ≥ 2 weeks, and/or night sweats ≥ 2 weeks	Any lung abnormality	Xpert. Culture on Xpert positive samples	Self-report	Yes	In participants eligible for sputum collection and a randomly selected subset of the others.
Gambia	43100/55832 (77.2)	Cough ≥ 2 weeks, Cough < 2 weeks with ≥ 2 other TB symptoms*, or No cough with ≥ 3 other TB symptoms*	Any lung or mediastinum abnormality	Smear and Culture. Xpert for survey TB cases	NA	Yes	Yes
Ghana	61726/67757 (91.1)	Cough ≥ 2 weeks	Any lung abnormality	Smear and Culture. Xpert on smear+ samples, and if cultures contaminated	Self-report	Fever, weight loss, and night sweats collected only in participants who had cough > 2 weeks, prevalent TB, or TB treatment	In participants who had cough ≥ 2 weeks, TB diagnosis, or treatment history
Indonesia	67944/76576 (88.7)	Cough ≥ 2 weeks and/or haemoptysis	Any lung or pleura abnormality	Smear and Culture. Xpert on smear+ and non-conclusive culture samples	Self-report	Yes	Yes
Lesotho	21719/26857 (80.9)	Cough ≥ 2 weeks, fever, weight loss, and/or night sweats	Any lung abnormality	Xpert and culture	NA	Yes	Yes
Malawi	31579/39026 (80.9)	Any symptoms** ≥ 1 week	Any lung abnormality	Smear and Culture. Xpert on smear+ or if culture contaminated	NA	Yes	Yes
Mongolia	50309/60031 (83.8)	Cough ≥ 2 weeks	Any lung abnormality	Smear and Culture, Xpert on smear+ samples	Self-report	Yes	Yes
Mozambique	32445/43442 (74.7)	Cough ≥2 weeks, blood in sputum, and/or any cough with one of the five symptoms/signs for ≥ 2 weeks***	Any lung or mediastinum abnormality or CAD4TB score ≥ 40	Smear, Xpert, and Culture	NA	Yes	In participants eligible for sputum collection and a randomly selected subset of the others.
Namibia	29495/38353 (76.9)	Cough, night sweats, fever, and/or weight loss	Any lung abnormality or CAD4TB score ≥60	Smear, Xpert, and Culture	Self-report	Yes	In participants eligible for sputum collection and a randomly selected subset of the others.
Nigeria	44186/77707 (56.8)	Cough ≥ 2 weeks	Any lung abnormality	Smear, culture, and Xpert	NA	Night sweats not collected.	Yes

Philippines	35191/53250 (66.1)	Cough ≥2 weeks, blood in the sputum, and/or haemoptysis	Any lung abnormality	Smear and Culture	Self-report	Yes	Yes
South Africa	46689/61466 (76)	Any cough, fever, night sweats, and/or weight loss	Any TB suggestive abnormality	Xpert Ultra and culture	Self-report	Yes	Yes
United Republic of Tanzania	50447/65664 (76.8)	Cough ≥ 2 weeks, haemoptysis, fever ≥2 weeks, weight loss, and/or night sweats	Any lung (or mediastinum) abnormality	Smear, culture, and Xpert A concern raised about the validity of the number of bacteriologically positive cases.	Self-report	Current cough not collected.	In participants eligible for sputum submission
Uganda	41154/45293 (90.9)	Cough ≥ 2 weeks	Any lung abnormality	Smear and culture. Xpert on smear+ samples	NA	Yes	Yes
Viet Nam	61763/87207 (70.8)	Productive cough ≥ 2 weeks	Any lung abnormality	Smear and culture	Self-report	Weight loss, fever, and night sweats were asked only in participants who were eligible for sputum submission.	In participants eligible for sputum submission

*Chest pain, night sweats, shortness of breath, loss of appetite, weight loss, fever, haemoptysis.
**Cough, sputum production, haemoptysis, chest pain, weight loss, night sweats, fatigue, fever, and shortness of breath.
***Chest pain, unexplained fever, night sweats, weight loss, and low mid-upper arm circumference
**** Current cough, fever, night sweats, and weight loss.
TB: tuberculosis; non-communicable diseases (NCDs)

Data on self-reported diabetes were collected in nine surveys.[151-157,164,166]All surveys provided data on current smoking vs non-current smoking, with 13 of them also including data on past smoking. Eight had information on alcohol use.[152,154-157,162,164] Only four surveys collected data on BMI.[152,155,156,158] None of the surveys reported on other NCD like CKD. In six of the surveys, NCD and their risk factors were recorded for only a subset of participants: those eligible for sputum collection and a randomly selected subset of others in Eswatini, Namibia, and Mozambique[155,157,165], those eligible for sputum collection in the United Republic of Tanzania, and Viet Nam,[156,166] and participants who had cough ≥ two weeks, had TB diagnosis, or treatment history in Ghana.[154] Consequently, there was a significant amount of missing data in these surveys, for instance, between 75.3% and 95.7% for diabetes (Table 4-2 and Figure 4-2). HIV status was collected in nine surveys, including three in which HIV status was sought only in a subset of the participants.[156,157,163] In the remaining six surveys, HIV status was missing from < 0.01% to 29.6%.

Figure 4-2.Proportion of missing data by variable and by survey



TB: tuberculosis; HIV: human immunodeficiency virus

Five surveys used the criterion of a cough ≥ two weeks as the sole symptom for screening before sputum.[152,154,158,163,166] Two other surveys used cough ≥ two weeks or blood in sputum/haemoptysis as the criteria.[151,153] The rest of the countries incorporated additional symptoms such as fever, weight loss, and night sweats in their screening algorithms. (Table 4-3)

Three surveys did not collect all of the four TB symptoms (current cough, fever, night sweats, and weight loss) required to define subclinical TB from all participants.[154,156,158] The United Republic of Tanzania did not collect data on current cough, while the survey in Nigeria did not collect night sweats. In Ghana, fever, weight loss, and night sweats were queried only among 2819 individuals who had a cough for more than two weeks, a diagnosis of prevalent TB, or a history of TB treatment. Similarly, in Vietnam, fever, weight loss, and night sweats data were collected solely from those eligible for sputum collection. To address these gaps, the presence or absence of any of the four symptoms was imputed using multi-level multiple imputation. Analyses that followed were based on these multiply imputed datasets. The subsequent analyses were based on multiply imputed datasets.

4.4.2. Characteristics of subclinical TB and symptomatic TB

The crude TB prevalence, not accounting for cluster sampling design, ranged from 0.28% in Bangladesh to 1.07% in the Philippines (Table 4-3). Among TB cases, 15.1% (Indonesia) to 56.7% (South Africa) met the definition of subclinical TB (median: 38.1%; interquartile range: 25.5- 48.2%).

Table 4-4 presents the characteristics of participants stratified by TB status: people without TB, those with subclinical TB, and those with symptomatic TB. The mean age was higher in people with subclinical TB (48.2 years) and symptomatic TB (45.9 years) than in those without TB (38.0 years). People meeting either TB case definition tended to be male, current smokers, HIV-positive and had a past history of TB than those without TB. Diabetes was most common in people with symptomatic TB (6.4%), and it was more common in people with subclinical TB (4.1%) than those without TB (2.8%).

Table 4-3.Crude prevalence of active TB and proportion of subclinical TB

Country	N	All TB (crude prevalence, %)	% Subclinical TB (95% CI)
Bangladesh	98710	280 (0.28)	40.3 (34.7-46.2)
Eswatini	24358	74 (0.30)	49.8 (38.1-61.5)
Gambia	43100	86 (0.20)	22.2 (14.0-33.3)
Ghana	61726	204 (0.33)	33.5 (24.5-43.8)
Indonesia	67944	433 (0.64)	15.1 (11.9-18.9)
Lesotho	21719	140 (0.64)	54.5 (45.8-62.9)
Malawi	31579	134 (0.42)	37.8 (29.9-46.4)
Mongolia	50309	253 (0.50)	51.6 (45.4-57.9)
Mozambique	32445	108 (0.33)	46.6 (36.1-57.3)
Namibia	29495	145 (0.49)	38.4 (30.3-47.1)
Nigeria	44186	255 (0.58)	19.9 (12.3-30.6)
Philippines	46689	501 (1.07)	27.3 (23.3-31.6)
South Africa	35191	260 (0.74)	56.7 (50.2-62.9)
United Republic of Tanzania	50447	176 (0.35)	35.5 (27.0-45.1)
Uganda	41154	162 (0.39)	23.6 (17.6-30.8)
Viet Nam	61763	232 (0.38)	41.8 (35.3-48.5)

Note: Values are based on multiply imputed datasets.
TB: tuberculosis; CI: confidence interval

Table 4-4.Characteristics of participants by TB status

Variable	Without TB	Subclinical TB	Symptomatic TB
Age, mean (SD)	38 (17·3)	48·2 (18·6)	45·9 (18·1)
Male, n (%)	312154 (42·3)	729 (60·9)	1440 (64·1)
Female, n (%)	425218 (57.7)	469 (39.1)	805 (35.9)
Current smoker, n (%)	144491 (19·6)	430 (35·9)	798 (35·5)
Past smoker, n (%)	43929 (6·0)	142 (11·8)	370 (16·5)
Alcohol drinking once a week or less, n (%)	166737 (22·6)	346 (28·9)	590 (26·3)
Alcohol drinking twice a week or more, n (%)	42903 (5·8)	117 (9·8)	213 (9·5)
*Diabetes, n (%)	20401 (2·8)	49 (4·1)	145 (6·4)
HIV-positive, n (%)	78569 (10·7)	207 (17·3)	427 (19·0)
Past history of TB, n (%)	24024 (3·3)	132 (11·0)	371 (16·5)

Note: Based on multiply imputed datasets. * Self-reported
TB: tuberculosis; SD: standard deviation

4.4.3. Associations between diabetes, NCD risk factors, and TB status

In the univariable model, older age, male gender, history of TB, current smoking, and HIV status were all associated with a higher likelihood of all TB combined. This was true when assessed separately for symptomatic and subclinical TB (Table 4-5). For instance, being male was associated with a doubled risk of TB: the odds ratio (OR) for subclinical TB was 2.14 (95% CI 1.89-2.42), and for symptomatic TB, it was 2.46 (95% CI 2.25-2.69). Current smoking was similarly associated with a 2-fold risk of TB (OR 2.24; 95% CI 1.94-2.60 for subclinical TB, and OR 2.21; 95% CI 2.00-2.44 for symptomatic TB) compared to those who were not current smokers. Moreover, individuals with a past history of smoking showed a higher likelihood of having either subclinical or symptomatic TB (OR 2.54; 95% CI 1.72-3.74 for subclinical TB, and OR 3.87; 95% CI 2.73-5.47 for symptomatic TB), compared to never smokers. Conversely, diabetes was linked to a two-fold increase in the risk of symptomatic TB (OR 2.30; 95% CI 1.63-3.25), but its association with subclinical TB was not significant (OR 1.42; 95% CI 0.85-2.35). Regarding alcohol consumption, the analysis indicated a greater likelihood of both subclinical and symptomatic TB, though with wide confidence intervals overlapping with null.

When age and gender were added to the model, the greatest risk elevation was observed in individuals with a past history of TB, associated with all TB types combined (OR 3.56; 95% CI 3.19-3.97), as well as both symptomatic (OR 4.19; 95% CI 3.70-4.75) and subclinical forms (OR 2.51; 95% CI 2.06-3.06). This was followed by a positive HIV status (Table 4-6). Current smoking remained significantly

associated with both subclinical (OR 1.62; 95% CI 1.38-1.90) and symptomatic TB (OR 1.49; 95% CI 1.34-1.66), whereas past smoking showed a significant association with symptomatic TB (OR 2.32; 95% CI 1.54-3.48) but not with subclinical TB (OR 1.41; 95% CI 0.91-2.18). Similar to the univariable model findings, diabetes was significantly associated with symptomatic TB (OR 1.67; 95% CI 1.17-2.40) but not with subclinical TB (OR 0.92; 95% CI 0.55-1.55).

Table 4-5.Associations between diabetes, NCD risk factors, and different manifestations of TB- multinomial logistic regression

	All TB		**Subclinical TB**		**Symptomatic TB**	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Current smoker vs non-current smoker	2.22 (2.04-2.43)	< 0.0001	2.24 (1.94-2.6)	<0.0001	2.21 (2.00-2.44)	< 0.0001
Past smoker vs never smoker	3.38 (2.41-4.73)	< 0.0001	2.54 (1.72-3.74)	<0.0001	3.87 (2.73-5.47)	< 0.0001
Alcohol drinking once a week or less vs no alcohol drinking	1.28 (0.95-1.73)	0.098	1.4 (1.02-1.94)	0.041	1.22 (0.88-1.68)	0.22
Alcohol drinking ≥ twice per week vs no alcohol drinking	1.77 (0.78-4.02)	0.16	1.86 (0.84-4.13)	0.12	1.72 (0.73-4.03)	0.2
Diabetes	1.99 (1.42-2.78)	0.00021	1.42 (0.85-2.35)	0.17	2.3 (1.63-3.25)	< 0.0001
Past history of TB	4.6 (4.14-5.12)	< 0.0001	3.33 (2.74-4.05)	< 0.0001	5.34 (4.72-6.03)	< 0.0001
HIV	2.31 (1.56-3.42)	0.0002	2.17 (1.41-3.33)	0.001	2.39 (1.58-3.61)	0.00022
Age per 10-year increase	1.29 (1.27-1.31)	< 0.0001	1.34 (1.3-1.38)	< 0.0001	1.26 (1.23-1.29)	< 0.0001
Male gender	2.34 (2.18-2.52)	< 0.0001	2.14 (1.89-2.42)	< 0.0001	2.46 (2.25-2.69)	< 0.0001

NCDs: non-communicable diseases; TB: tuberculosis; CI: confidence interval; HIV: human immunodeficiency virus

Table 4-6.Associations between diabetes, NCD risk factors, and different manifestations of TB, adjusted for age and gender

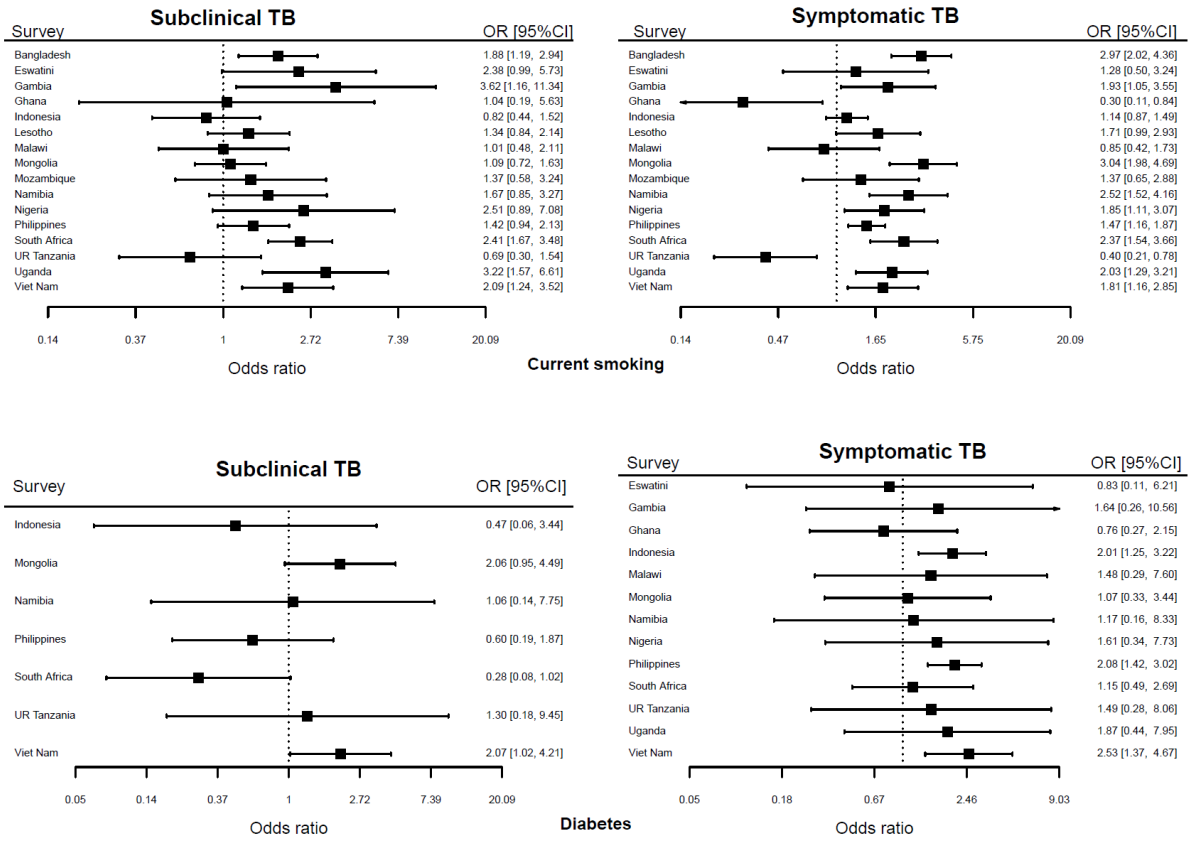
	All TB		Subclinical TB		Symptomatic TB	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Current smoker vs non-current smoker	1.53 (1.39-1.69)	< 0.0001	1.62 (1.38-1.9)	< 0.0001	1.49 (1.34-1.66)	< 0.0001
Past smoker vs never smoker	1.97 (1.33-2.91)	0.0016	1.41 (0.91-2.18)	0.12	2.32 (1.54-3.48)	0.00028
Alcohol drinking once a week or less vs no alcohol drinking	1.2 (0.91-1.58)	0.18	1.33 (0.98-1.8)	0.065	1.14 (0.84-1.54)	0.38
Alcohol drinking ≥ twice per week vs no alcohol drinking	1.49 (0.64-3.48)	0.34	1.59 (0.7-3.62)	0.26	1.43 (0.59-3.46)	0.41
Diabetes	1.39 (0.98-1.97)	0.063	0.92 (0.55-1.55)	0.75	1.67 (1.17-2.4)	0.0064
Past history of TB	3.56 (3.19-3.97)	< 0.0001	2.51 (2.06-3.06)	< 0.0001	4.19 (3.7-4.75)	< 0.0001
HIV	2.39 (1.6-3.57)	0.00017	2.21 (1.42-3.43)	0.001	2.5 (1.64-3.81)	0.00016

NCDs: non-communicable diseases; TB: tuberculosis; CI: confidence interval; HIV: human immunodeficiency virus

In the model adjusted for age and gender, the point estimates for alcohol drinking ≥ twice per week vs no alcohol drinking were consistent with an increased risk for both, but the confidence intervals were wide, overlapping the null.

For the association between current smoking and subclinical TB, I^2 was 47.2% (95% CI 5.5-70.5). (Figure 4-3). I^2 was larger for the association between current smoking and symptomatic TB (I^2 = 76.5%; 95% CI 62.0-85.4). Nonetheless, the direction of the association was consistently above one in all but three surveys (Ghana, Malawi, and the United Republic of Tanzania) with wide confidence intervals. For alcohol drinking, diabetes, and HIV, between-study heterogeneity contributed minimally to little total variation due to a large within-study variance (Figures 4-3, 4-4, 4-5, 4-6, 4-7). When restricted to HIV-negative participants, the associations between smoking and all TB and with subclinical and symptomatic TB remained similar (Table 4-7). The subgroup analysis required excluding surveys where HIV status was not collected; they included four surveys that collected diabetes (Ghana, Indonesia, Philippines, and Viet Nam). In this subgroup, the analysis did not reveal any significant associations between diabetes and all forms of TB, including both subclinical and symptomatic TB.

Figure 4-3.The associations between current smoking/diabetes and TB status by survey



Note: Results of multivariable multiple regression models adjusted for age and gender by survey
Surveys with large standard errors resulting in 95% confidence intervals ranging from 0 to infinity or for which the model failed to converge are excluded.
TB: tuberculosis; OR: odds ratio; CI: confidence intervals

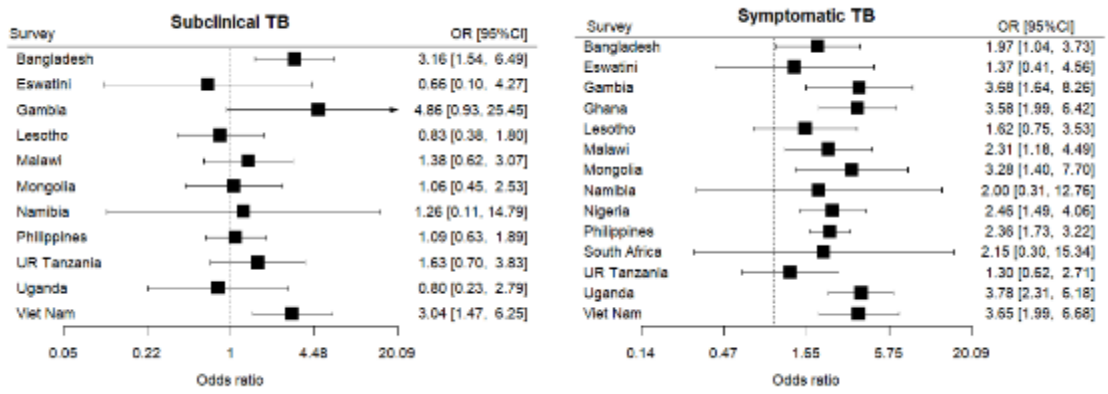
Current smoking

Subclinical TB: I-squared=47·2% (95% CI 5·5-70·5), p=0·019, tau^2=0·08; Symptomatic TB: I-squared=76·5% (95% CI 62-85·4), p<0.0001, tau^2=0·24;

Diabetes

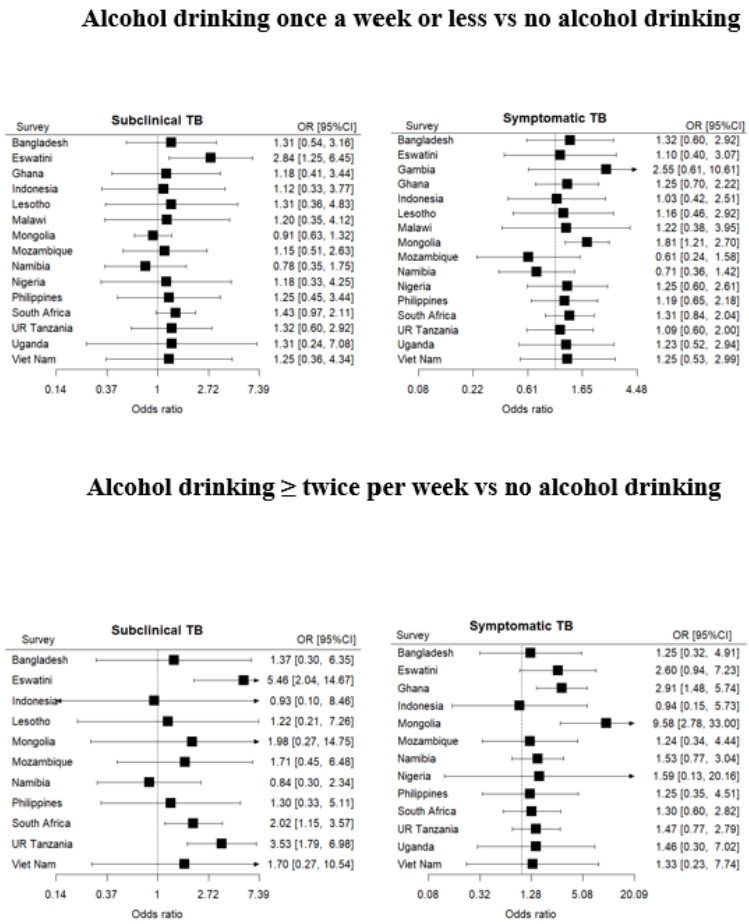
Subclinical TB: I-squared=0% (95% CI 0-52·3), p=0.74, tau^2=0.37; Symptomatic TB: I-squared=0% (95% CI 0-52·3), p=0.8, tau^2=0.011

Figure 4-4.Past smoking and TB status by survey



Subclinical TB: I-squared = 4.2% (95% CI 0-54.3), p = 0.4, tau^2 = 0.13; Symptomatic TB: I-squared = 0% (95% CI 0-52.3), p = 0.61, tau^2 = 0.0027
Surveys with large standard errors resulting in 95% confidence intervals ranging from 0 to infinity or for which the model failed to converge are excluded (Subclinical TB: Ghana, Indonesia, Mozambique, Nigeria, South Africa; symptomatic TB: Indonesia and Mozambique).
TB: tuberculosis; OR: odds ratio; CI: confidence intervals

Figure 4-5.Alcohol drinking and TB status by survey



Note: Results of multivariable multiple regression models adjusted for age and gender by survey

Surveys with large standard errors resulting in 95% confidence intervals ranging from 0 to infinity or for which the model failed to converge are excluded (Subclinical TB: Gambia, Ghana, Malawi, Nigeria, Uganda; symptomatic TB: Gambia, Lesotho, and Malawi).

TB: tuberculosis; OR: odds ratio; CI: confidence intervals

Alcohol drinking once a week or less vs no alcohol drinking

Subclinical TB: I-squared = 0% (95% CI 0-52.3), p=0.91, $tau^2 = 0.01$

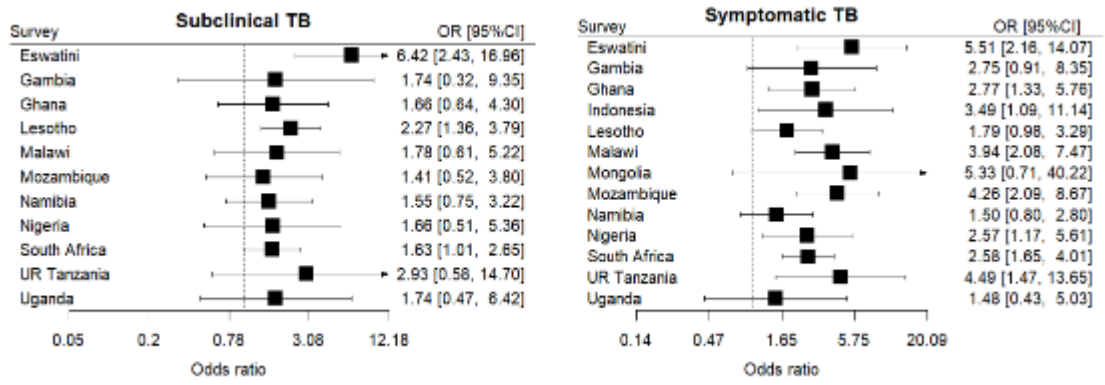
Symptomatic TB: I-squared = 0% (95% CI 0-52.3), p=0.65, $tau^2 = 0.021$

Alcohol drinking once a week or less vs no alcohol drinking

Subclinical TB: I-squared = 0% (95% CI 0-52.3), p=0.93, $tau^2 = 0.23$

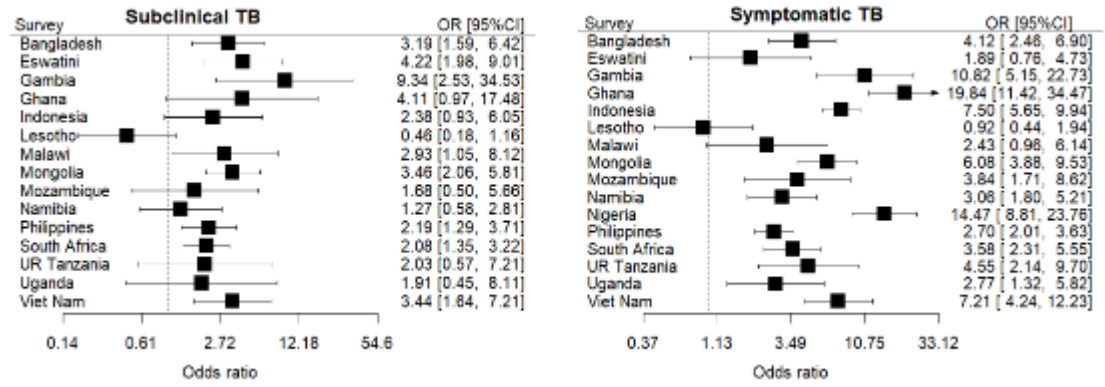
Symptomatic TB: I-squared = 0% (95% CI 0-52.3), p=0.65, $tau^2 = 0.021$

Figure 4-6.HIV status and TB status by survey



Note: Results of multivariable multiple regression models adjusted for age and gender by survey
Surveys with large standard errors resulting in 95% confidence intervals ranging from 0 to infinity or for which the model failed to converge are excluded (Subclinical TB: Indonesia, Lesotho, Mongolia, Philippines, Viet Nam; symptomatic TB: Lesotho, Philippines, Viet Nam).
TB: tuberculosis; OR: odds ratio; CI: confidence intervals
Subclinical TB: I-squared = 0% (95% CI 0-52.3), p = 0.93, $tau^2 = 0$
Symptomatic TB: I-squared = 0% (95% CI 0-52.3), p = 0.62, $tau^2 = 0.027$

Figure 4-7.Past history of TB and TB status by survey



Note: Results of multivariable multiple regression models adjusted for age and gender by survey
Surveys with large standard errors resulting in 95% confidence intervals ranging from 0 to infinity or for which the model failed to converge are excluded (Subclinical TB: Nigeria; symptomatic TB).
TB: tuberculosis; OR: odds ratio: CI: confidence interval
Subclinical TB: I-squared = 42.74% (95% CI 0-68.3), p = 0.036, $tau^2 = 0.15$
Symptomatic TB: I-squared = 86.14% (95% CI 79-90.8), p < 0.0001, $tau^2 = 0.5$

Table 4-7.Associations between diabetes, NCD risk factors, and different manifestations of TB, adjusted for age and sex, in HIV-negative individuals

	All TB		Subclinical TB		Symptomatic TB	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Current smoker vs non-current smoker	1.72 (1.47-2.01)	<0.0001	1.76 (1.4-2.21)	<0.0001	1.68 (1.37-2.07)	<0.0001
Past smoker vs never smoker	1.65 (1.12-2.41)	0.012	1.29 (0.78-2.14)	0.32	1.97 (1.24-3.1)	0.0044
Alcohol drinking once a week or less vs no alcohol drinking	1.13 (0.77-1.66)	0.52	1.19 (0.82-1.74)	0.35	1.08 (0.68-1.72)	0.74
Alcohol drinking ≥ twice per week vs no alcohol drinking	1.4 (0.85-2.32)	0.18	1.41 (0.83-2.41)	0.2	1.38 (0.73-2.6)	0.31
Diabetes	1.1 (0.71-1.69)	0.67	1.1 (0.56-2.13)	0.78	1.08 (0.61-1.91)	0.79
Past history of TB	2.26 (1.83-2.79)	<0.0001	1.7 (1.22-2.37)	0.0019	2.76 (2.13-3.58)	<0.0001

NCDs: non-communicable diseases; TB: tuberculosis; CI: confidence interval ; HIV : human immunodeficiency virus

4.4.4. Sensitivity analysis

When using different categorisations of alcohol drinking, estimates remained imprecise, with wide confidence intervals overlapping one; thus, it was difficult to see a difference in the results compared to the primary categorisation (Table 4-8).

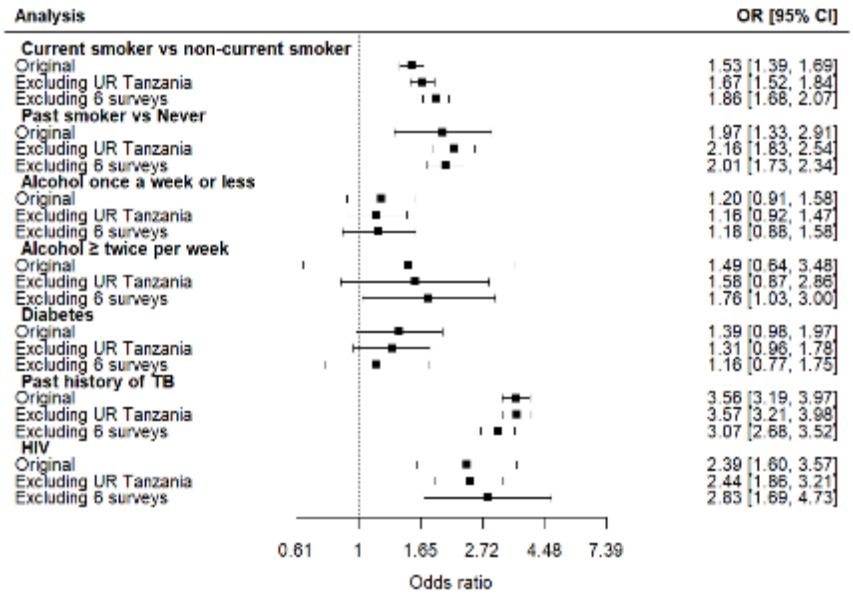
Table 4-8.Sensitivity analysis using different categorisations of alcohol drinking

Definition	Outcome	Odds ratio (95% CI)	p-value
*Alcohol drinking once a week or less vs no alcohol drinking	All TB	1.2 (0.91-1.58)	0.18
	Subclinical TB	1.33 (0.98-1.8)	0.065
	Symptomatic TB	1.14 (0.84-1.54)	0.38
*Alcohol drinking ≥ twice per week vs no alcohol drinking	All TB	1.49 (0.64-3.48)	0.34
	Subclinical TB	1.59 (0.7-3.62)	0.26
	Symptomatic TB	1.43 (0.59-3.46)	0.41
Any alcohol drinking vs no drinking	All TB	1.27 (0.85-1.89)	0.23
	Subclinical TB	1.39 (0.93-2.07)	0.1
	Symptomatic TB	1.21 (0.8-1.83)	0.36
Alcohol drinking ≥ twice per week vs less	All TB	1.41 (0.64-3.1)	0.37
	Subclinical TB	1.46 (0.68-3.13)	0.31
	Symptomatic TB	1.38 (0.6-3.15)	0.43

*Primary analysis
Estimates are adjusted for age and gender.
TB: tuberculosis; CI: confidence interval

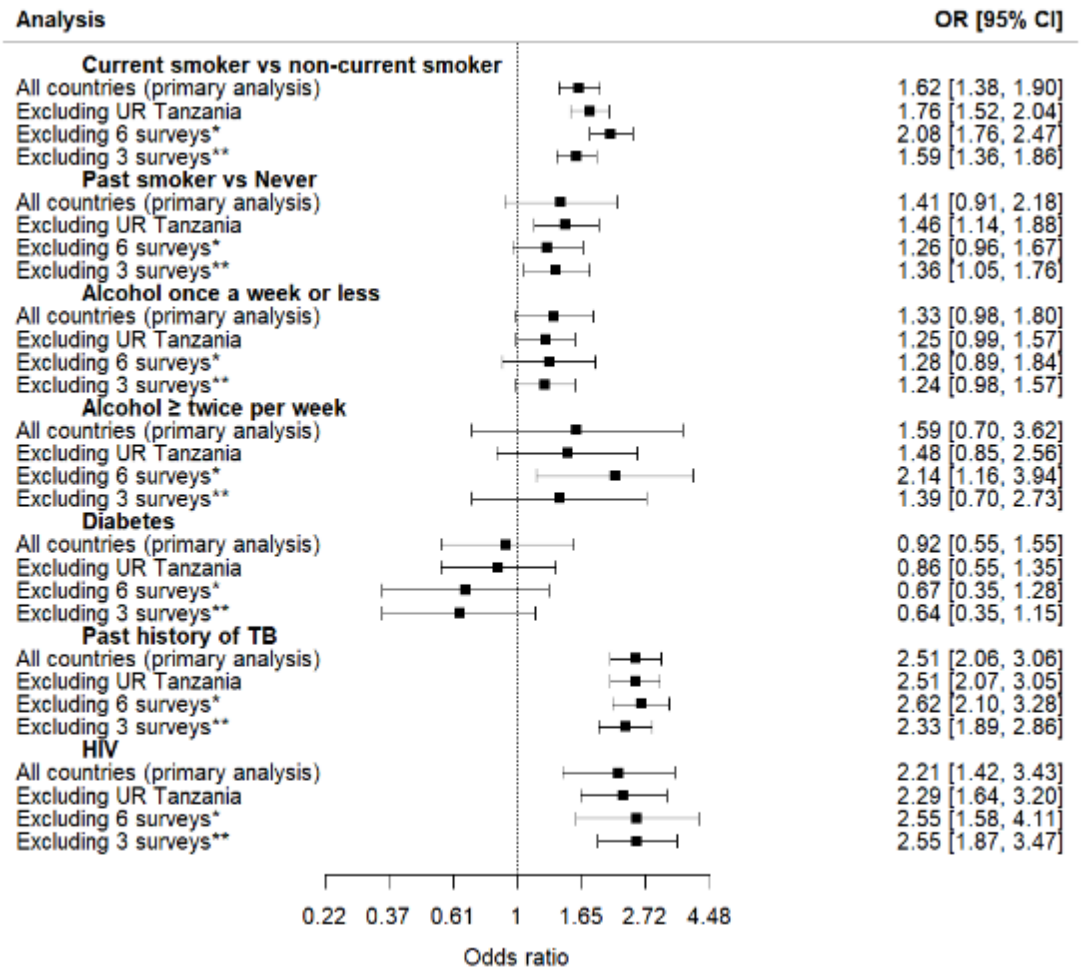
I conducted a comparative analysis of the estimated odds ratios from the primary analysis with those derived from excluding Tanzania, excluding six surveys that only collected NCD data for a subset of participants, and removing three surveys that did not collect all four essential symptoms (Figure 4-8, 4-9, 4-10). For current smoking, excluding the six countries increased point estimates marginally (OR 1.49; 95% CI 1.34-1.66 in the primary analysis for symptomatic TB VS. OR 1.75; 95% CI 1.54-1.98). Overall, the odds ratios for past TB history showed a decrease upon excluding these six countries (e.g. OR 4.19; 95% CI 3.70-4.75 in the primary analysis for symptomatic TB VS. OR 3.35; 95% CI 2.85-3.95). Excluding these surveys also resulted in an increased odds ratio for the link between alcohol consumption ≥ twice per week and subclinical TB (OR 2.14; 95% CI 1.16-3.94). A similar trend was observed when the analysis was limited to three studies with minimal missing data on alcohol consumption. (Table 4-9). Apart from these observations, the sensitivity analyses did not yield significantly different estimates.

Figure 4-8.Sensitivity analysis for the associations between all TB and predictors adjusted for age and gender



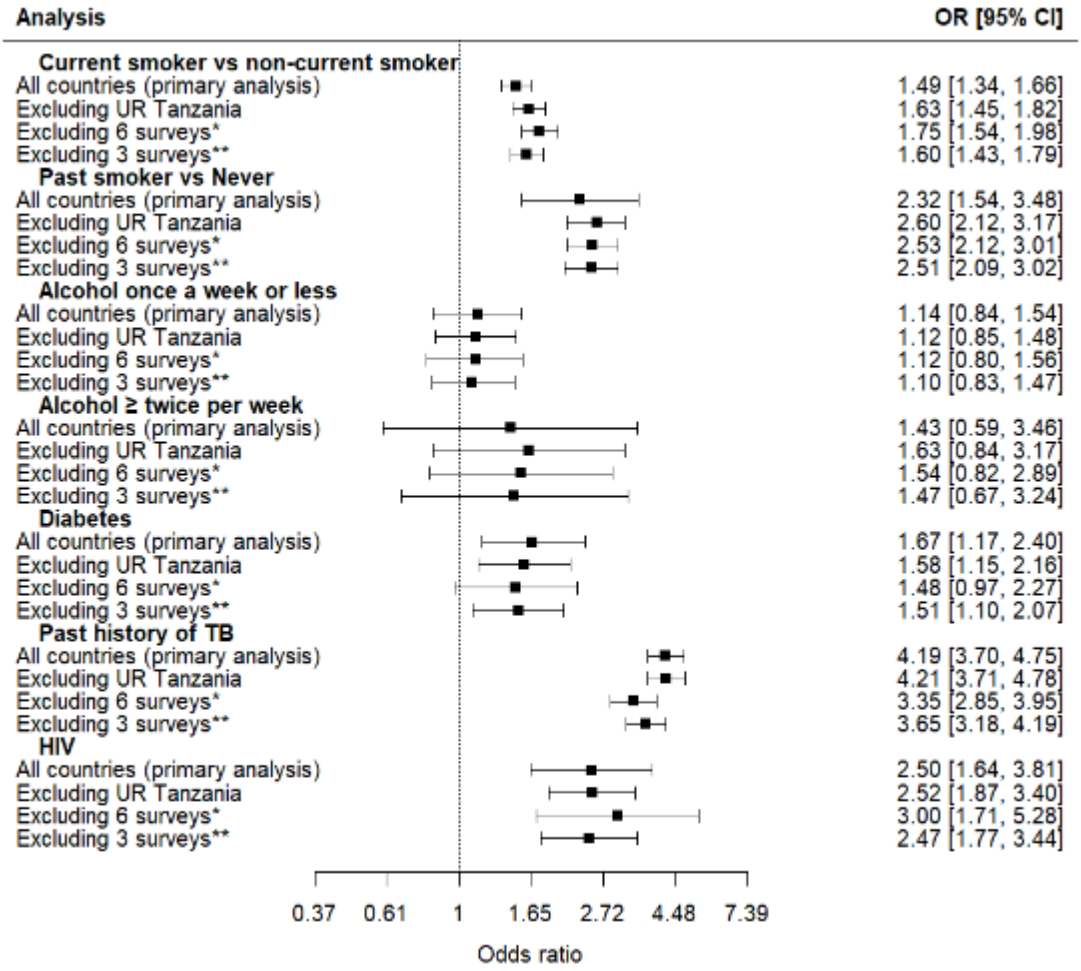
*Excluding 6 surveys (Eswatini, Ghana, Mozambique, Namibia, United Republic of Tanzania, Viet Nam) that collected NCD data only in a subset of participants.
TB: tuberculosis; HIV: human immunodeficiency virus; CI: confidence interval; OR: odds ratio; UR: United Republic of

Figure 4-9.Sensitivity analysis for the associations between subclinical TB and predictors adjusted for age and gender



*Excluding 6 surveys (Eswatini, Ghana, Mozambique, Namibia, United Republic of Tanzania, Viet Nam) that collected NCD data only in a subset of participants.
** Excluding 3 surveys (Nigeria, United Republic of Tanzania, Viet Nam) that did not collect all four TB symptoms.
TB: tuberculosis; HIV: human immunodeficiency virus; CI: confidence interval; OR: odds ratio; UR: United Republic of

Figure 4-10.Sensitivity analysis for the associations between symptomatic TB and predictors adjusted for age and gender



*Excluding 6 surveys (Eswatini, Ghana, Mozambique, Namibia, United Republic of Tanzania, Viet Nam) that collected NCD data only in a subset of participants.
** Excluding 3 surveys (Nigeria, United Republic of Tanzania, Viet Nam) that did not collect all four TB symptoms.

TB: tuberculosis; HIV: human immunodeficiency virus; CI: confidence interval; OR: odds ratio; UR: United Republic of

Table 4-9. Associations between diabetes, NCD risk factors, and different manifestations of TB, adjusted for age and sex, restricting to surveys with minimal missing data

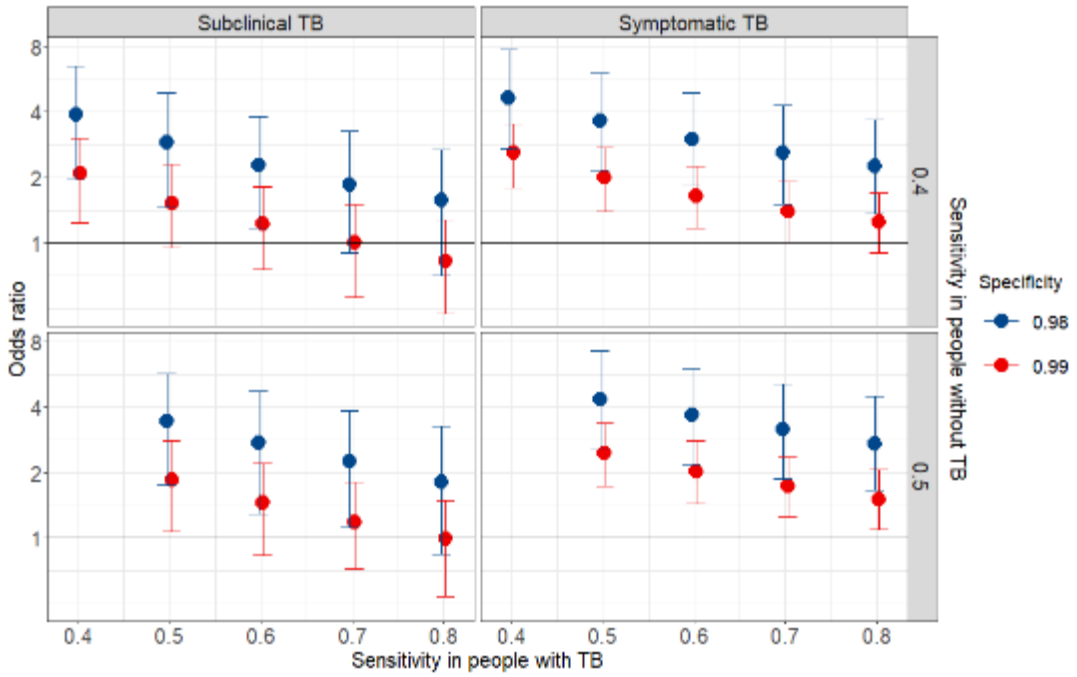
	All TB		Subclinical TB		Symptomatic TB	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Alcohol drinking once a week or less vs no alcohol drinking	1.31 (1.08-1.59)	0.0068	1.35 (1.04-1.77)	0.026	1.27 (0.98-1.65)	0.072
Alcohol drinking ≥ twice per week vs no alcohol drinking	1.73 (1.14-2.62)	0.0099	2.19 (1.29-3.72)	0.0035	1.3 (0.69-2.45)	0.42
Diabetes	1.43 (1.12-1.81)	0.0039	0.74 (0.42-1.28)	0.28	1.78 (1.36-2.34)	<0.0001

NCDs: non-communicable diseases; TB: tuberculosis; CI: confidence interval

For alcohol drinking, the analysis was restricted to three surveys (Gambia, Mongolia, and South Africa), for diabetes, to four surveys (Indonesia, Mongolia, Philippines, and South Africa).

Figure 4-11 illustrates the results of a sensitivity analysis that examines the effects of misclassifying diabetic status. Generally, as the sensitivity of self-reported diabetes among individuals with TB increases (indicating a higher likelihood of diabetes diagnosis in TB patients), the ORs tend to decrease. This pattern indicates that the actual ORs might be underestimated in scenarios where diabetes is underdiagnosed. In the context of symptomatic TB, the lower bounds of the uncertainty intervals remained consistently above one, except in cases where there was a substantial disparity in sensitivity (40% in those without TB versus ≥ 70% in those with TB), combined with a 99% specificity. Conversely, for subclinical TB, the true relationship with diabetes appeared to be positive in most scenarios, unlike the association observed using the originally reported diabetic status. This was particularly evident when the specificity was set at 98%, suggesting that the primary analysis using self-reported diabetes underestimated the actual association.

Figure 4-11.Sensitivity analysis-impact of misclassification of diabetic status



Odds ratios are adjusted for age and gender. Points and error bars indicate median and simulation intervals (2.5th and 97.5th percentiles of the estimates).
Odds ratios in the analysis using original diabetic status: Subclinical TB: 0.91 (95% CI 0.54-1.51); Symptomatic TB: 1.65 (95% CI 1.16- 2.35)

4.5. Discussion

My IPD meta-analysis of TB prevalence survey data suggests that alongside a history of TB and HIV, factors such as self-reported diabetes and current smoking could be used to identify people who are more likely to have prevalent TB, independent of age and gender. The associated risk was approximately 1.5 times greater for both current smoking for both symptomatic and subclinical TB and self-reported diabetes in cases of symptomatic TB. These findings could be instrumental in guiding screening policies and strategies. Despite the higher risk associated with HIV and previous TB history, the prevalence of diabetes and current smoking in some regions exceeds or is comparable to that of HIV or previous TB. For instance, in the Philippines, HIV prevalence is below 1%, while the rates of current smoking are 6.5% among women and 39% among men, and diabetes prevalence stands at 7%.2 Therefore, systematically screening individuals with these risk factors could identify more people with TB. While screening for TB among people with diabetes has been advocated for over a decade,[131] only half of the 30 high TB burden countries have incorporated it into their guidelines, and there's limited data on its implementation.[188] Moreover, current smoking was associated with both symptomatic and subclinical TB. This suggests current smokers could be prioritised for chest X-rays in addition to symptom screening.

Interestingly, self-reported diabetes was associated with an increased likelihood of symptomatic TB but not with subclinical TB. This aligns with studies included in previous reviews that indicate a 1.5 to 3 times higher risk of TB in individuals with diabetes.[12,13] Such studies, primarily cohort and case-control studies, often rely on TB diagnoses made through routine care, which are predominantly symptomatic. A review by Al-Rifai included three cross-sectional studies assessing the relationship between TB and NCDs;[13,189-191] none of them implemented systematic TB screening. Instead, they used TB diagnosis based on past TB history, symptoms suggestive of TB, or diagnoses made in routine care. Consequently, the relationships observed in these earlier studies are more likely applicable to symptomatic TB cases. It has been suggested in the literature that TB tends to present more severely and is more likely to be symptomatic in individuals with

diabetes compared to those without. [192,193] However, data regarding the risk of subclinical TB in people with diabetes is scarce. My primary analysis suggests that the risk of subclinical TB might not be elevated in people with diabetes, implying that chest X-ray screening in asymptomatic individuals with diabetes may not significantly exceed yields expected from TB prevalence rates in the general population. Nevertheless, this does not entirely negate the utility of X-rays, considering the balance between expected yields and resource availability. It is important to also acknowledge the wide confidence intervals in both the pooled and country-specific estimates. Additionally, as highlighted in the sensitivity analysis, the associations could be underestimated due to the reliance on self-reported diabetes. Therefore, while the increased risk of subclinical TB in people with diabetes is not conclusively dismissed, the degree of risk might be lower than that associated with symptomatic TB.

The observed TB risk linked to current smoking varied substantially across different surveys, potentially influenced by varying social contexts. For instance, smoking might be more common in environments with a higher risk of TB exposure, like bars. While my study did not aim for causal inference, it is plausible that lifestyle factors and other confounders contributed to this association. Nonetheless, the identified increased risk implies that current smokers might have a higher prevalence of both subclinical and symptomatic TB compared to the general population. The increased TB risk suggests that targeted, systematic screening among smokers could be effective in identifying otherwise undiagnosed TB cases. However, due to this heterogeneity, it is crucial for countries to consider their specific data and contextual factors rather than relying solely on pooled estimates. Notably, two countries, Ghana and Tanzania, showed statistically significant inverse associations. This could be attributed to biases arising from collecting smoking history only from selected participants, such as those eligible for sputum submission. In Ghana, additional symptoms apart from cough were only recorded for individuals with a cough lasting ≥ two weeks, a TB diagnosis, or a history of TB treatment. Other possible explanations for these inverse associations include the cessation of smoking among symptomatic individuals and the likelihood of chance

findings, as indicated by the wide confidence intervals and the multitude of analyses conducted.

In the primary analysis, the relationship between alcohol consumption and TB was unexpectedly not significant. However, in a sensitivity analysis that excluded studies with substantial missing data, alcohol drinking showed a significant association with TB, although the risk magnitude did not markedly differ. This indicates that the insignificant finding in the primary study may lack robustness due to the extent of missing data, leaving the association between alcohol consumption and prevalent TB inconclusive.

Although it was not the main scope of my review, my findings reaffirmed the existing understanding that males have a higher likelihood of TB. However, males were underrepresented in all the surveys analyzed. This implies that during community-based screening initiatives, men might be less inclined to participate, potentially diminishing the overall effectiveness of these screenings. Therefore, it is crucial for screening programs to actively engage male individuals to enhance both the yield and cost-effectiveness of these activities.

The primary strength of my study lies in its substantial sample size, encompassing over 700,000 individuals. This sample was drawn from nationally representative surveys in both Asian and African countries with high TB incidence rates. Additionally, having access to IPD allowed for a standardized definition of subclinical TB. However, the study is not without its limitations.

First, the diagnosis of diabetes relied on self-reporting, which, while highly specific, has low sensitivity and likely results in under-detection. [184,185] For example, a Demographic and Health Survey in South Africa found a diabetes prevalence of 13% in men and 8% in women based on HbA1c measurements, significantly higher than the 5% and 4% reported through self-report, indicating underdiagnosis. Despite the limitation, my sensitivity analysis demonstrated the robustness of the association between diabetes and symptomatic TB. Furthermore, it is important to note that laboratory-based diabetes screening may not always be practical or

available in community-based TB screening settings. In this context, inquiring about self-reported diabetes could serve as a convenient method to identify individuals at a higher risk of TB, particularly in areas with a high prevalence of diabetes. The risk magnitude identified in my study based on self-reported diabetes could then be utilised to estimate the potential increase in screening yields in such settings. However, the strength of the risk association identified in my review might not be fully generalisable to contexts where diabetes is systematically screened.

Second, not all surveys collected data on alcohol use and diabetes. To address this, I employed multi-level multiple imputation to fill in these data gaps. While six surveys gathered information on diabetes, alcohol, and smoking from only a subset of participants, three of these surveys collected it from all individuals eligible for sputum submission as well as a randomly selected group of others. Therefore, my imputation model, which included criteria for sputum submission eligibility, was likely to effectively impute missing data without bias, assuming a reasonable mechanism of missingness (missing at random conditional on all observed variables). Additionally, my sensitivity analysis revealed no significant variations in the results, reinforcing the robustness of my approach. Similarly, HIV status was not consistently recorded across all surveys, and when it was, there were instances of sporadic missingness, often due to participant refusal. However, the influence of non-response bias in national surveys is generally not substantial.[194]

Third, three surveys (Ghana, Nigeria, and the United Republic of Tanzania) did not gather all four symptoms indicative of TB, which were required for defining symptomatic vs subclinical TB. While the presence of any one of the four symptoms was sufficient to classify an individual as symptomatic, the absence of other symptoms made it impossible to define symptomatic status, indicating that missingness of symptomatic status was not at random. While multi-level modelling, borrowing information from other surveys, helped recover information, there remains a potential for bias. Nevertheless, the consistency of my findings in the sensitivity analyses offers some reassurance.

Fourth, my multi-level multiple imputation did not incorporate clustering within households. As a result, the imputation model was not entirely aligned with the analysis model, which did include random household effects. This discrepancy may have introduced minor biases, particularly in the estimation of standard errors. However, to my knowledge, no available software could allow for this while retaining all the flexibility of my approach. Therefore, my method likely represents the most practical alternative for minimizing bias.

Fifth, all surveys collected sputum only when participants met specific screening criteria, including chest X-ray findings and symptoms. Although this is in line with WHO-recommended standard methodologies for TB prevalence surveys, [143] it is possible that cases of subclinical TB without apparent lung shadows were missed. However, where there was variability in symptom screening criteria across surveys, nearly all studies used any lung abnormality detected in chest X-rays as a criterion, which ensures a high sensitivity of about 95%.[195] [196]

Sixth, although intended, I could not investigate TB risk arising from the presence of overlapping risk factors and NCD. Other than diabetes, other NCD known to be associated with TB, such as CKD and chronic respiratory disease, were missing. The substantial amount of missing data for certain variables, coupled with the relatively small number of identified TB cases, precluded more sophisticated analyses, such as integrating interaction terms in the models. Standardising the collection of NCD-related variables in future TB prevalence surveys, in line with the WHO STEPwise approach,[175] could fill the gap. Such standardisation would pave the way for developing models to estimate individual TB risk, including subclinical forms, using multivariable modelling techniques. Given the observed heterogeneity in risk factors in my analysis, the collection and incorporation of local data become even more crucial to enable the prediction of individual TB applicable to local settings.

4.6. Conclusion

This study suggests that people who have self-reported diabetes and current smokers are more likely to have symptomatic TB. Up to 50% of TB can be subclinical, and people who smoke are more likely to have subclinical TB, independent of age and gender. Current smokers might warrant intensified screening, such as the use of chest X-rays, taking into account the expected yields. Future surveys should consider the collection of NCD-related variables systematically to enable more granular analysis and develop a model to predict individual TB risk associated with NCDs.

5. Prevalence of non-communicable diseases in households affected by tuberculosis: an individual participant data meta-analysis of contact tracing studies

5.1. Abstract

Background

Household contacts of people diagnosed with TB are at a high risk of TB infection and disease and additionally share risk factors for other health conditions, particularly NCD. In TB prevalence surveys, diabetes was the only NCD reported, and its diagnosis was based on self-report. To address this limitation, I conducted a systematic review and IPD meta-analysis of contact tracing studies to investigate the prevalence of NCD among household contacts of people with TB.

Method

I searched Medline, Embase and the Global Index Medicus from inception to 16 May 2023. I included studies that assessed for at least one NCD among household contacts of people with clinical TB. I estimated the NCD prevalence through mixed effects logistic regression, including studies providing IPD and by conducting aggregated data meta-analyses.

Results

I identified 39 eligible studies, of which 14 provided IPD (29,194 contacts). Of the remaining 25 studies, 18 studies reported aggregated data suitable for meta-analysis. The pooled prevalence of diabetes in studies that undertook biochemical testing was 8.8% (95% CI, 5.1-14.9%, four studies). Age-and sex-standardised prevalence was numerically higher in two studies (13.2 vs 10.2% and 11.5 vs 8.4%) than the corresponding national estimates and similar in two studies. The prevalence of diabetes known based on self-report or medical records was 3.4% (95% CI 2.6-4.6%, 14 studies). The prevalence did not significantly differ by the availability of IPD. Data on other NCD were limited.

Conclusion

The prevalence of diabetes among household contacts was high, while that of known diabetes was substantially lower, suggesting underdiagnosis. Integrating diabetes screening within household contact investigations may help fill this gap. While I aimed to assess other NCD, data using standard diagnostic methods were lacking. The lack of data reinforces the need for a prospective study applying systematic screening for common NCD to accurately estimate their burden.

5.2. Introduction

A systematic review of TB prevalence surveys in the previous chapter showed that smoking and alcohol drinking were more common among individuals living with people with TB than those not living with them. On the other hand, the review did not show a difference in the NCD prevalence. The use of data from TB prevalence surveys is helpful in understanding the prevalence of TB risk factors such as smoking; however, the largest limitation in TB prevalence surveys was the reliance on participants' self-report to ascertain NCD.

Recent studies reported the prevalence of diabetes among household contacts using laboratory tests.[140,141] Such studies using objective methods to ascertain NCD allow a more accurate understanding of the burden of NCD in household contacts. However, no systematic review exists that synthesised the body of evidence.

Therefore, I conducted a systematic review and IPD meta-analysis of contact tracing studies to evaluate the prevalence of NCD among household contacts of people with TB.

5.3. Methods

The protocol of this systematic review has been pre-registered (CRD42021248455). The review was conducted and reported following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD).[180]

5.3.1. Search strategy

I included studies that assessed household contacts of people with clinical TB for at least one NCD in LMIC. NCD of interest were: diabetes, hypertension, renal disease, cardiovascular disease, chronic respiratory disease, dyslipidaemia, cancer, and mental health conditions. I appraised case definitions of NCDs and included studies regardless of the NCD ascertainment method. A person with

clinical TB was defined as someone diagnosed with either bacteriologically-confirmed TB or clinically diagnosed TB, in accordance with study definitions. Household contacts were as defined by the study authors. I included cross-sectional studies, cohort studies, case-control studies, and cohorts nested within randomised or non-randomised trials. I excluded studies with less than ten index people diagnosed with clinical TB. The review was restricted to studies from LMIC (i.e. low, lower-middle, and upper-middle income) at the time the study was conducted as defined by the World Bank.[197]

5.3.2. Eligibility criteria and search strategy

I searched for eligible studies from inception to 16 April 2021 using Medline (OVID), Embase and the Global Index Medicus, and the search was updated on 16 May 2023. Additionally, abstracts of the following international conferences were searched for the last five years: the Union World Conference on Lung Health, the American Thoracic Society Conference, and the European Respiratory Society International Congress. Reference lists of included papers were additionally reviewed. No language limitation was applied. I used a validated search filter to identify studies in low and middle-income countries.[198] Appendix 1 presents a detailed search strategy developed in consultation with a librarian.

5.3.3. Study selection and data extraction

I and another reviewer screened titles and abstracts of identified records independently. Two reviewers independently reviewed full-text articles selected through the screening process. Any discrepancies between the two reviewers were resolved through discussions.

I requested IPD from the study authors and collected the following information: 1). Methods: study design, study context (setting, location), date of the study, and recruitment of participants; 2) Participants: N, age, smoking history, alcohol use, comorbidities, TST/IGRA positivity, bacteriological status of TB cases (e.g. smear and Xpert), HIV status, the definition of households, socioeconomic status of

households, and use of biomass fuel; and 3) Outcomes: diabetes, hypertension, renal disease (or chronic kidney disease), cardiovascular disease, chronic respiratory disease, dyslipidemia, cancer, and mental disease.
To be included in the final analysis, datasets needed to include age, gender, and at least one type of NCD.

I made at least two attempts to contact the study authors. For studies where IPD could not be obtained, I extracted aggregated data from study papers for the above variables.

5.3.4. Quality assessment

I assessed the quality of the included studies using an adapted version of the National Institute of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies.[199] The tool assessed 1) the participation rate of index people with clinical TB and 2) of contacts; 3) the diagnostic method of clinical TB (bacteriologically confirmed as per the WHO definition.[200] I did not use commonly used assessment tools such as ROBINS-E and Newcastle Ottawa scale as they are intended for studies with control groups examining associations rather than prevalence.

5.3.5. Outcomes

I defined diabetes as (i) known diabetes (based self-report history or medical records without definition) or (ii) diabetes newly identified through fasting plasma glucose ≥ 7mmol/L, random blood glucose ≥ 11.1mmol/L, 2-h glucose ≥ 200 mg/dL (based on oral glucose tolerance tests), or HbA1c ≥ 6.5%. Given the limited number of studies that used blood tests, I also analysed known diabetes separately. I intended to include both type 1 and 2 diabetes, while none of the included studies specified the type. I defined hypertension as either systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90mmHg, or self-reported hypertension. If multiple measurements were available, I intended to take a mean, but none of the included studies reported multiple measurements. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60

ml/min/1.73m^2. I also included renal diseases as per the study authors' definition, anticipating the limited availability of data based on eGFR. For other NCD, I followed the definitions used by individual studies as it was not possible to harmonise classifications across included studies.

5.3.6. Statistical analysis

Handling of missing data

I conducted multiple imputation by multilevel fully-conditional specifications to impute both outcomes and predictors.[201] For each outcome, I conducted multiple imputations separately, restricting to studies that reported the outcome. This imputed sporadically missing outcomes and sporadically and systematically missing predictors. The imputation models included random intercepts for studies and for households where household identifiers were available to account for clustering.

In the primary imputation model, I performed imputation merging studies with and without household identifiers. I assigned the same household identifiers to all study participants in studies where household identifiers were not available, and the model included random intercepts for households and studies. The imputation model included NCD, age, and sex of both contacts and among index people with TB. However, the above imputation model did not converge for diabetes and hypertension; thus, for these outcomes, I performed multiple imputation in two ways: 1) restricting to studies with household identifiers and 2) including all studies. For studies with household identifiers, the model included NCD, age, and sex of both contacts and among index people with TB. When including all studies, I included random intercepts for studies only, and the model included age, sex, smoking, alcohol use, body mass index, diabetes, known diabetes, and hypertension. I generated 20 multiply imputed data sets with 20 iterations between successive imputations. I assessed model convergence visually. All primary analyses were performed across multiply imputed datasets; the necessary analytic

models were fitted on each imputed dataset, and their outputs were combined using Rubin's rules.

Prevalence of NCD based on IPD meta-analysis

I estimated the prevalence of individual NCD in contacts aged ≥ 15 years. I conducted the analyses in two ways: 1) accounting for clustering within households using generalised estimating equations restricted to studies with household identifiers and 2) not accounting for it by including all studies. Because these two approaches showed similar results, I primarily reported the results based on the full dataset, ignoring clustering within households. I used mixed effects logistic regressions to estimate prevalence accounting for clustering within studies. I presented prevalence estimates in each study in forest plots and reported the I-squared statistic. I conducted a sub-group analysis by region.
Next, I compared the prevalence of diabetes alone (due to limited data on other NCD) with the national estimated prevalence using age and sex standardization. I estimated the standardised prevalence adjusted for age and sex using country-specific population estimates in 2019.[4] This was compared with national estimates of diabetes prevalence from the 2019 Global Burden of Disease study, standardised for age and sex.

To standarise the diabetes prevalence from my study and the national estimated prevalence for age and sex, age was categorised into five-year intervals between 15 and ≥ 55 years. In cases where some age groups did not have any participants in a study, and hence it was not possible to estimate age and sex-stratified prevalence for all strata, I merged adjacent age groups as necessary to allow weighting. However, one study included only contacts aged 30 years or older. To maintain consistency, I restricted the corresponding national estimate to individuals aged ≥ 30 years.

Finally, I compared the prevalence of each NCD between contacts with and without TB. The pooled prevalence was estimated for each group through one-stage meta-

analysis. I also estimated OR through mixed effects logistic regressions to assess the association between TB status and NCD prevalence.

Association between NCD in index persons with TB and contacts

I aimed to determine whether contacts of index individuals with an NCD are more likely to have the same NCD compared to contacts of those without an NCD, exploring the potential clustering of NCDs. In the presence of clustering, screening could potentially be prioritised to households whose index persons have NCD. To investigate this, I employed a multilevel logistic regression model using NCD status among index persons as a predictor and that among contacts as the outcome. The model incorporated random intercepts for both studies and households. The association between NCD presence in index people with TB and their contacts was represented using odds ratios as pooled random effect estimates. Given that the age and gender of index individuals are likely to be correlated with those of their contacts and the prevalence of NCD, I also included the age and sex of index persons with TB as covariates. Subsequently, I adjusted the model to include the age and sex of the contacts. This was to determine if contacts of index individuals with NCDs are more likely to have the same NCD, compared to those of the same age and sex whose index persons do not have NCD rather than to show a causal association. Hence, I did not adjust for other potential confounders.

Sensitivity analysis

My primary imputation model assigned the same household identifiers to all participants in studies where these identifiers were not available. This might have artificially increased the correlations between participants, as they were treated as if they were from the same household. To address this, I repeated the analysis of NCD prevalence using an alternative multiple imputation that ignored clustering within households.

Next, I repeated the analyses, excluding studies with missing data on outcomes in > 50% of contacts.

Lastly, I conducted a quantitative bias analysis using IPD. The quantitative bias analysis aimed to explore how misclassifying diabetes status impacted the observed association between known diabetes among index people with TB and known diabetes among contacts.[146] I estimated and presented the true associations between diabetes among index people with TB and diabetes among contacts after correcting misclassification due to the use of known diabetes. I assumed various levels of accuracy (i.e. sensitivity and specificity) of known diabetes for contacts (outcome) and index people with TB (exposure) at the same time. Based on the literature reporting the accuracy of self-reported diabetes, I varied the sensitivity of known diabetes from 40% to 80%.[147-150] The prevalence of known diabetes in contacts in the study population was 2.6%, consistent with a high specificity reported elsewhere.[147,148] Thus, I tested a specificity of 98% and 99%. I assumed the same level of sensitivity and specificity between contacts and index people with TB since members of the same households are likely to share similar access to health care and the likelihood of diabetes diagnosis. Instead, my analysis focused on assessing the impact of non-differential and differential misclassification depending on the diabetes status of other members of the household. In the case of differential misclassification, I varied the sensitivity of known diabetes among index people with TB by diabetes status of contacts and the sensitivity among contacts by diabetes status of index people with TB. I assumed that the extent of differential misclassification was the same between index people with TB and contacts.

I adapted the approach described by Fox et al. while using fixed levels of sensitivity and specificity.[146] I selected one of the 20 imputed datasets and estimated positive and negative predictive values for diabetes, given their observed status. Second, using the predictive values, I simulated a new variable representing the bias-adjusted diabetes status, drawing randomly from a Bernoulli distribution. I generated the bias-adjusted diabetes status for contacts and then for index people with TB using bias-adjusted data in contacts sequentially. I fitted a logistic regression model using the bias-adjusted diabetes status in contacts as an outcome and that in index people with TB as a predictor, adjusted for age and sex.

Finally, to account for random errors, I sampled a standard normal deviate and multiplied it by the standard error of the bias-adjusted association and combined it with the point estimate from the model. I repeated the above process 1000 times and presented the median and 2.5th and 97.5th percentiles as uncertainty intervals.

Meta-analysis of aggregated data

To explore the bias due to data availability, I conducted an aggregated data meta-analysis of the prevalence of NCD using studies without IPD. For studies with IPD, I pooled estimates using multiply imputed datasets. I performed a random-effects meta-analysis using the restricted maximum likelihood estimator stratified by the availability of IPD. I ignored clustering within households because it was not possible with studies without IPD. I-squared statistics and tau^2 were presented.

Assessment of reporting biases

I assessed publication bias by creating a funnel plot proposed by Hunter et al. if there were at least ten studies in the meta-analysis.[202] I assessed the degree of asymmetry using Egger's tests.

5.3.7. Ethics

This IPD meta-analysis was approved by the UCL Research Ethics Committee (21569/001). All participants provided informed consent to participate in the primary studies included in this meta-analysis.

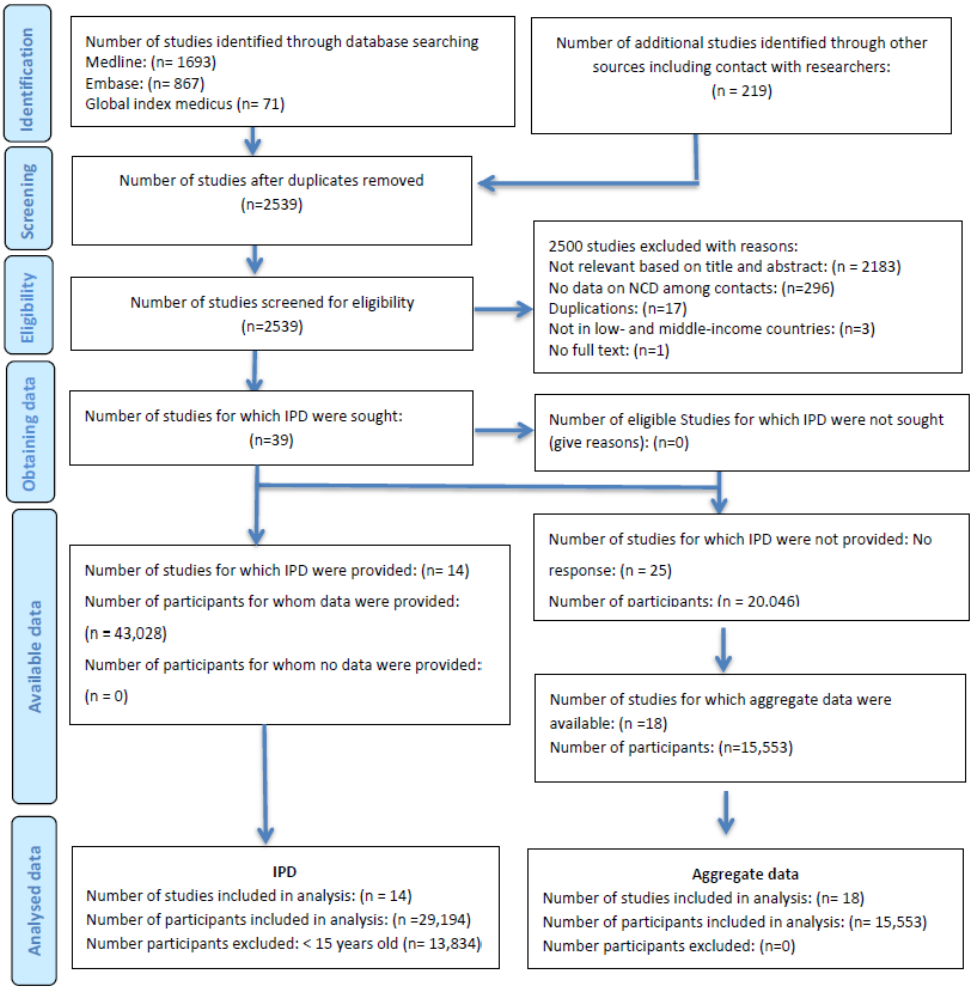
5.4. Results

5.4.1. Search results and study characteristics

From the review of 2,537 records identified, 37 studies were considered potentially eligible, and their IPD were sought; 12 provided IPD (Figure 5-1).[203-213] Additionally, one study was identified through contacting experts[214] and one through conference abstract searching[141], from which the authors provided IPD.

Thus, IPD from 14 studies were included, comprising 29,194 contacts; 11 of them included data on 8260 index people with TB.

Figure 5-1.Study selection



	IPD		Aggregated data	
Outcomes	# studies included	# participants included	# studies included	# participants included
Diabetes	4	8680	6	5404
Known diabetes	14	29194	12	8506
Hypertension	4	17303	2	1107
Cardiovascular disease	4	12383	0	0
Renal disease	6	14229	3	1784
Depression	1	838	0	0

Among 25 studies (N = 20,046) for which IPD could not be obtained, aggregated data could be extracted from 18 studies (N =15,553).[215-232] The remaining seven studies did not report the prevalence of individual NCD among contacts.
Among 14 studies with IPD, five were from Peru[203,206,207,210,212] and the rest in various countries (Table 5-1).

Table 5-1. Characteristics of studies with individual participant data

Study	Country	N	Definition of household contacts	Diagnosis of diabetes	Other non-communicable diseases
Acuna-Villaorduna, 2022	Brazil	894	Sleeping under the same roof ≥5 days/week, sharing meals ≥5 days/week, watching TV together on week nights or weekends, or other significant contact (85% of these visited the household ≥18 days/month)	Not defined	Renal disease; not defined.
Becerra, 2019	Peru	521	Lived in the same household as an index patient at the time the index person was enrolled in the study were invited to participate.	Not defined	Hypertension, renal disease, heart disease; all of them were not defined.
Bekken, 2020	India	144	Living ≥75% of the time in the same household as the index person with TB and sharing the same kitchen	Not defined	Not reported
Diaz, 2021	Colombia	138	Not reported	Self-report	Not reported
Galea, 2022	Peru	838	Living in the same household as an index person with TB at the time the index subject is enrolled in the study	Not defined	Depression defined as Patient Health Questionnaire-9 scores 5-27. Heart disease and hypertension not defined.
Grandjean, 2011	Peru	1113	Any individual who lived with the index case for >1 day each week in the period during which the index person was symptomatic with TB disease.	Not defined	Renal disease and heart disease; both of them were not defined.
Grandjean, 2015	Peru	620	Any person living in the same house as the index person for > 1 day a week	Not defined.	Not reported.
Marin, 2017	Colombia	2464	Had spent time regularly (weekly) in the same household as the index person for at least a month prior to the time when the index person's diagnosis was confirmed.	Not defined	Renal disease. “Health status upon enrolment was established by physical examination performed by a physician and specific enquiry on immunosuppressive conditions related to medication intake and concurrent diseases.”
Martinson, 2021	South Africa	6695	All individuals who shared dwelling airspace by either having slept overnight at least once, or shared at least two meals in the same household as the index person in the 14 days prior to the index person’s diagnosis of TB	RBG and self-reported	Hypertension (BP measurement and known diagnosis). Only a subset of contacts (9.7%) had a BP measurement.
Restrepo, 2018*	South Africa	323	Sharing at least 5 h per week in a house or closed space with a person with confirmed pulmonary TB.	RBG and point-of-care HbA1c in all.	Hypertension, renal disease, and heart disease; all were not defined.

Shivakumar, 2018	India	359	Resided with an adult with TB for at least 3 months before their TB diagnosis in their household	All tested for HbA1c. DM was defined as previously diagnosed, self-reported DM or HbA1c ≥ 6.5%	Renal disease; not defined.
Shu, 2017	Peru	174	Adult contacts of the index person who spent at least one day per week with the patient.	Not defined	Not reported
Verrall, 2022	Indonesia	1383	Had lived with the index person for >5 hours a week and had no previous TB.	RBG in all and HbA1c for all tested for RBG >100	Not reported
Vo, 2023	Viet Nam	2079	Persons sharing a kitchen with the index person for one or more nights in the past three months prior to treatment initiation of the index person.	Not defined	Not reported

*The study reported data from the Texas-Mexico border and South Africa but I included data from South Africa only.

BP: blood pressure; TB: tuberculosis; RBG: random blood glucose; DM: diabetes

Across studies, the median age of contacts was 35 years, and the majority of contacts (59.1%) were female (Table 5-2). Characteristics of participants by studies are available in Table 5-3. Data on diabetes were available in four,[141,209,211,214] and known diabetes in all studies.

Table 5-2.Demographic and clinical characteristics of contacts and index people with TB

	Studies	Participants	N (%) or median [IQR]	Missing, N (%)
Contacts				
Age (median [IQR])	14	29194	35 [23-51]	0 (0)
Male (%)	14	29194	11933 (40.9)	1 (0)
Current smoker (%)	11	24499	2489 (10.2)	6348 (25.9)
Alcohol use (%)	9	23279	5824 (25)	5745 (24.7)
BMI (median [IQR])	7	10927	23.5 [20.6-27.3]	5800 (53.1)
HIV-positive (%)	14	29194	491 (1.7)	7468 (25.6)
Diabetes (%)	4	8680	226 (2.6)	5760 (66.4)
Known diabetes (%)	14	29194	661 (2.3)	6774 (23.2)
Hypertension (%)	4	17303	1459 (8.4)	5860 (33.9)
Cardiovascular disease (%)	4	12383	332 (2.7)	444 (3.6)
Renal disease (%)	6	14229	511 (3.6)	1247 (8.8)
Depression (%)	1	838	184 (22)	0 (0)
Tuberculosis (%)	8	22745	352 (1.5)	5253 (23.1)
Index people with TB				
Age (median [IQR])	11	8260	32 [23-46]	39 (0.5)
Male (%)	11	8260	4969 (60.2)	38 (0.5)
Diabetes (%)	6	3659	18.8 [16.7-21.5]	152 (4.2)
Known diabetes (%)	5	3924	1826 (46.5)	584 (14.9)
Hypertension (%)	8	7754	536 (6.9)	295 (3.8)
Cardiovascular disease (%)	4	6057	551 (9.1)	399 (6.6)
Renal disease (%)	2	3702	84 (2.3)	210 (5.7)
Depression (%)	3	4108	132 (3.2)	220 (5.4)

Note: Raw data before imputation

BMI: body mass index; IQR: interquartile range

Table 5-3.Characteristics of participants by study

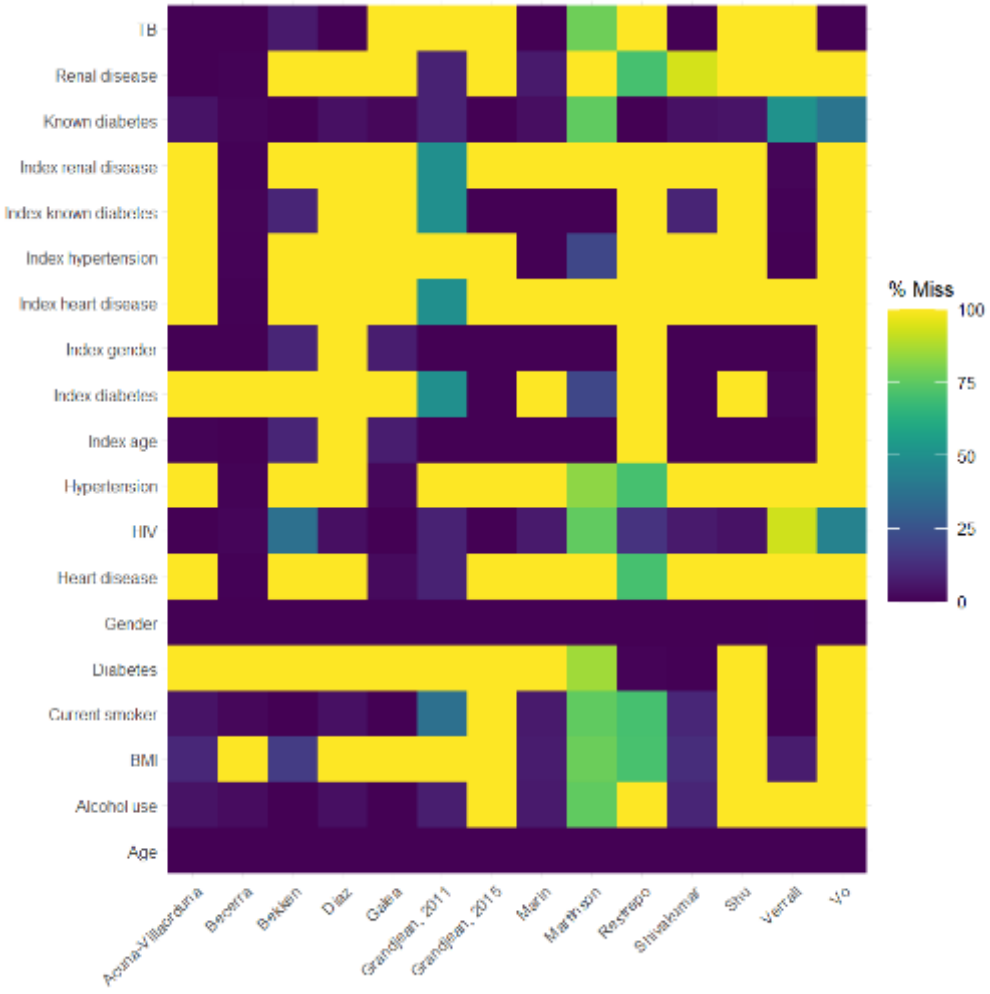
	Acuna-Villaorduna	Becerra	Bekken	Diaz	Galea	Grandjean, 2011	Grandjean, 2015	Marin	Martinson	Restrepo	Shivakumar	Shu	Verrall	Vo
Contacts														
N	601	9447	328	1512	838	1775	2420	1318	6695	323	765	196	897	2079
Age (median [IQR])	33.00 [22.00, 48.00]	34.00 [23.00, 49.00]	33.00 [22.00, 48.00]	40.00 [26.00, 56.00]	38.00 [25.00, 50.00]	32.00 [23.00, 48.00]	34.00 [23.00, 50.00]	36.00 [23.00, 50.00]	33.00 [22.00, 52.00]	49.00 [38.50, 55.00]	34.00 [23.00, 44.00]	35.00 [26.00, 49.00]	35.00 [24.00, 50.00]	47.00 [32.00, 59.00]
Gender (%)														
Female	345 (57.4)	5488 (58.1)	204 (62.2)	870 (57.5)	493 (58.8)	917 (51.7)	1254 (51.8)	814 (61.8)	4222 (63.1)	229 (70.9)	440 (57.5)	123 (62.8)	515 (57.4)	1346 (64.7)
Male	256 (42.6)	3959 (41.9)	124 (37.8)	642 (42.5)	345 (41.2)	858 (48.3)	1166 (48.2)	504 (38.2)	2473 (36.9)	94 (29.1)	325 (42.5)	73 (37.2)	381 (42.5)	733 (35.3)
NA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Current smoker (%)														
No	361 (60.1)	8428 (89.2)	203 (61.9)	1380 (91.3)	775 (92.5)	1067 (60.1)	0 (0.0)	848 (64.3)	1382 (20.6)	34 (10.5)	621 (81.2)	0 (0.0)	563 (62.8)	0 (0.0)
Yes	211 (35.1)	875 (9.3)	125 (38.1)	74 (4.9)	63 (7.5)	58 (3.3)	0 (0.0)	383 (29.1)	244 (3.6)	61 (18.9)	63 (8.2)	0 (0.0)	332 (37.0)	0 (0.0)
NA	29 (4.8)	144 (1.5)	0 (0.0)	58 (3.8)	0 (0.0)	650 (36.6)	2420 (100.0)	87 (6.6)	5069 (75.7)	228 (70.6)	81 (10.6)	196 (100.0)	2 (0.2)	2079 (100.0)
Alcohol use (%)														
No	379 (63.1)	5634 (59.6)	313 (95.4)	1391 (92.0)	617 (73.6)	587 (33.1)	0 (0.0)	969 (73.5)	1271 (19.0)	0 (0.0)	549 (71.8)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	194 (32.3)	3532 (37.4)	15 (4.6)	64 (4.2)	221 (26.4)	1047 (59.0)	0 (0.0)	260 (19.7)	354 (5.3)	0 (0.0)	137 (17.9)	0 (0.0)	0 (0.0)	0 (0.0)
NA	28 (4.7)	281 (3.0)	0 (0.0)	57 (3.8)	0 (0.0)	141 (7.9)	2420 (100.0)	89 (6.8)	5070 (75.7)	323 (100.0)	79 (10.3)	196 (100.0)	897 (100.0)	2079 (100.0)
BMI (median [IQR])	24.28 [21.37, 27.66]	NA [NA, NA]	19.33 [17.87, 20.82]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	23.73 [21.26, 26.67]	24.34 [20.90, 29.67]	26.21 [22.36, 32.65]	23.02 [20.09, 26.50]	NA [NA, NA]	23.08 [20.55, 26.43]	NA [NA, NA]
HIV (%)														
No	601 (100.0)	9283 (98.3)	208 (63.4)	1449 (95.8)	835 (99.6)	1610 (90.7)	2401 (99.2)	1230 (93.3)	1239 (18.5)	272 (84.2)	701 (91.6)	185 (94.4)	62 (6.9)	1159 (55.7)
Yes	0 (0.0)	54 (0.6)	0 (0.0)	6 (0.4)	3 (0.4)	3 (0.2)	19 (0.8)	1 (0.1)	383 (5.7)	4 (1.2)	13 (1.7)	2 (1.0)	3 (0.3)	0 (0.0)
NA	0 (0.0)	110 (1.2)	120 (36.6)	57 (3.8)	0 (0.0)	162 (9.1)	0 (0.0)	87 (6.6)	5073 (75.8)	47 (14.6)	51 (6.7)	9 (4.6)	832 (92.8)	920 (44.3)
Diabetes														
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	884 (13.2)	270 (83.6)	695 (90.8)	0 (0.0)	845 (94.2)	0 (0.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	57 (0.9)	51 (15.8)	69 (9.0)	0 (0.0)	49 (5.5)	0 (0.0)
NA	601 (100.0)	9447 (100.0)	328 (100.0)	1512 (100.0)	838 (100.0)	1775 (100.0)	2420 (100.0)	1318 (100.0)	5754 (85.9)	2 (0.6)	1 (0.1)	196 (100.0)	3 (0.3)	2079 (100.0)

Known diabetes (%)														
No	552 (91.8)	9106 (96.4)	320 (97.6)	1409 (93.2)	789 (94.2)	1595 (89.9)	2382 (98.4)	1223 (92.8)	1585 (23.7)	284 (87.9)	708 (92.5)	172 (87.8)	425 (47.4)	1209 (58.2)
Yes	20 (3.3)	240 (2.5)	8 (2.4)	44 (2.9)	36 (4.3)	18 (1.0)	38 (1.6)	51 (3.9)	41 (0.6)	39 (12.1)	25 (3.3)	14 (7.1)	18 (2.0)	69 (3.3)
NA	29 (4.8)	101 (1.1)	0 (0.0)	59 (3.9)	13 (1.6)	162 (9.1)	0 (0.0)	44 (3.3)	5069 (75.7)	0 (0.0)	32 (4.2)	10 (5.1)	454 (50.6)	801 (38.5)
Hypertension (%)														
No	0 (0.0)	8520 (90.2)	0 (0.0)	0 (0.0)	755 (90.1)	0 (0.0)	0 (0.0)	0 (0.0)	649 (9.7)	60 (18.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	0 (0.0)	875 (9.3)	0 (0.0)	0 (0.0)	69 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	480 (7.2)	35 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NA	601 (100.0)	52 (0.6)	328 (100.0)	1512 (100.0)	14 (1.7)	1775 (100.0)	2420 (100.0)	1318 (100.0)	5566 (83.1)	228 (70.6)	765 (100.0)	196 (100.0)	897 (100.0)	2079 (100.0)
Heart disease (%)"														
No	0 (0.0)	9103 (96.4)	0 (0.0)	0 (0.0)	804 (95.9)	1607 (90.5)	0 (0.0)	0 (0.0)	0 (0.0)	93 (28.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	0 (0.0)	309 (3.3)	0 (0.0)	0 (0.0)	15 (1.8)	6 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NA	601 (100.0)	35 (0.4)	328 (100.0)	1512 (100.0)	19 (2.3)	162 (9.1)	2420 (100.0)	1318 (100.0)	6695 (100.0)	228 (70.6)	765 (100.0)	196 (100.0)	897 (100.0)	2079 (100.0)
Renal disease (%)"														
No	599 (99.7)	8898 (94.2)	0 (0.0)	0 (0.0)	0 (0.0)	1609 (90.6)	0 (0.0)	1222 (92.7)	0 (0.0)	94 (29.1)	49 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	2 (0.3)	495 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)	0 (0.0)	9 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NA	0 (0.0)	54 (0.6)	328 (100.0)	1512 (100.0)	838 (100.0)	162 (9.1)	2420 (100.0)	87 (6.6)	6695 (100.0)	228 (70.6)	716 (93.6)	196 (100.0)	897 (100.0)	2079 (100.0)
Depression (%)														
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	654 (78.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	184 (22.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NA	601 (100.0)	9447 (100.0)	328 (100.0)	1512 (100.0)	0 (0.0)	1775 (100.0)	2420 (100.0)	1318 (100.0)	6695 (100.0)	323 (100.0)	765 (100.0)	196 (100.0)	897 (100.0)	2079 (100.0)
TB (%)														
No	566 (94.2)	9235 (97.8)	291 (88.7)	1509 (99.8)	0 (0.0)	0 (0.0)	0 (0.0)	1318 (100.0)	1413 (21.1)	0 (0.0)	742 (97.0)	0 (0.0)	0 (0.0)	2066 (99.4)
Yes	35 (5.8)	212 (2.2)	15 (4.6)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	51 (0.8)	0 (0.0)	23 (3.0)	0 (0.0)	0 (0.0)	13 (0.6)
NA	0 (0.0)	0 (0.0)	22 (6.7)	0 (0.0)	838 (100.0)	1775 (100.0)	2420 (100.0)	0 (0.0)	5231 (78.1)	323 (100.0)	0 (0.0)	196 (100.0)	897 (100.0)	0 (0.0)
Index people with TB														
N	159	3298	171	NA	293	404	686	361	1992	NA	436	54	406	NA
Age (median [IQR])	35.00 [24.00, 44.75]	27.00 [21.00, 42.00]	45.00 [30.00, 52.50]		26.00 [21.00, 44.00]	28.00 [23.00, 39.00]	28.00 [21.00, 42.00]	36.00 [24.00, 50.00]	37.00 [28.00, 48.00]		38.00 [27.00, 49.00]	25.50 [20.00, 37.75]	41.00 [30.25, 52.00]	
Gender (%)														

No	52 (32.7)	1321 (40.1)	29 (17.0)		114 (38.9)	168 (41.6)	273 (39.8)	154 (42.7)	771 (38.7)		156 (35.8)	24 (44.4)	191 (47.0)	
Yes	107 (67.3)	1977 (59.9)	126 (73.7)		157 (53.6)	236 (58.4)	413 (60.2)	207 (57.3)	1221 (61.3)		280 (64.2)	30 (55.6)	215 (53.0)	
NA	0 (0.0)	0 (0.0)	16 (9.4)		22 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Diabetes (%)														
No	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	181 (44.8)	646 (94.2)	0 (0.0)	89 (4.5)		318 (72.9)	0 (0.0)	280 (69.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	23 (5.7)	40 (5.8)	0 (0.0)	1523 (76.5)		118 (27.1)	0 (0.0)	122 (30.0)	
NA	159 (100.0)	3298 (100.0)	171 (100.0)		293 (100.0)	200 (49.5)	0 (0.0)	361 (100.0)	380 (19.1)		0 (0.0)	54 (100.0)	4 (1.0)	
Known diabetes (%)														
No	0 (0.0)	3080 (93.4)	138 (80.7)		0 (0.0)	181 (44.8)	646 (94.2)	332 (92.0)	1919 (96.3)		311 (71.3)	0 (0.0)	316 (77.8)	
Yes	0 (0.0)	186 (5.6)	17 (9.9)		0 (0.0)	23 (5.7)	40 (5.8)	29 (8.0)	73 (3.7)		80 (18.3)	0 (0.0)	88 (21.7)	
NA	159 (100.0)	32 (1.0)	16 (9.4)		293 (100.0)	200 (49.5)	0 (0.0)	0 (0.0)	0 (0.0)		45 (10.3)	54 (100.0)	2 (0.5)	
Hypertension (%)														
No	0 (0.0)	3107 (94.2)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	354 (98.1)	1297 (65.1)		0 (0.0)	0 (0.0)	349 (86.0)	
Yes	0 (0.0)	169 (5.1)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	7 (1.9)	318 (16.0)		0 (0.0)	0 (0.0)	57 (14.0)	
NA	159 (100.0)	22 (0.7)	171 (100.0)		293 (100.0)	404 (100.0)	686 (100.0)	0 (0.0)	377 (18.9)		436 (100.0)	54 (100.0)	0 (0.0)	
Heart disease (%)														
No	0 (0.0)	3204 (97.1)	0 (0.0)		0 (0.0)	204 (50.5)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Yes	0 (0.0)	84 (2.5)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
NA	159 (100.0)	10 (0.3)	171 (100.0)		293 (100.0)	200 (49.5)	686 (100.0)	361 (100.0)	1992 (100.0)		436 (100.0)	54 (100.0)	406 (100.0)	
Renal disease (%)														
No	0 (0.0)	3162 (95.9)	0 (0.0)		0 (0.0)	202 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	392 (96.6)	
Yes	0 (0.0)	119 (3.6)	0 (0.0)		0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	11 (2.7)	
NA	159 (100.0)	17 (0.5)	171 (100.0)		293 (100.0)	200 (49.5)	686 (100.0)	361 (100.0)	1992 (100.0)		436 (100.0)	54 (100.0)	3 (0.7)	
Depression (%)														
No	0 (0.0)	0 (0.0)	0 (0.0)		129 (44.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)		142 (48.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
NA	159 (100.0)	3298 (100.0)	171 (100.0)		22 (7.5)	404 (100.0)	686 (100.0)	361 (100.0)	1992 (100.0)		436 (100.0)	54 (100.0)	406 (100.0)	

The availability of other NCD was variable (Table 5-2, Table 5-3, Figure 5-2). In seven studies with data, 0.2 to 5.8% of contacts were diagnosed with TB.

Figure 5-2.Proportion of missing data by study



The quality of individual studies is summarised in Table 5-4. In ten studies with IPD, > 50% of index people with TB were enrolled, suggesting an acceptable representation of households with TB. Eleven studies included index TB patients with bacteriological confirmation. All but one study provided a clear definition of household contacts. Three studies used a combination of blood glucose and HbA1c, and one used blood glucose alone.[141,209,211] Diabetes status was missing in 75.6% (5069/6695) in one study;[214] however, the other three studies had < 1% of missing data.[141,209,211] One study defined depression as Patient Health Questionnaire-9 scores ≥ 5.[212] Ascertainment methods of

other diseases were insufficiently defined (Table 5-1). Characteristics of studies without IPD are presented in Table 5-5.

Table 5-4.Quality assessment of individual studies

IPD	Author year	1. Was the objective of the study to estimate the prevalence of any NCD among contacts?	1. Was the participation rate of the index patients at least 50%	2.Was the index patients bacteriologically diagnosed?	3.Was the household contacts clearly defined?	4. Was NCD ascertained using laboratory tests or using objective measurement?	5. Was >80% of contacts who met eligibility criteria assessed?
Yes	Acuna-Villaorduna, 2022	No	Yes	Yes	Yes	No	Yes
Yes	Becerra, 2019	No	Yes	Yes	Yes	No	No information
Yes	Bekken, 2020	No	Yes	Yes	Yes	No	Yes
Yes	Diaz, 2021	No	Yes	No information	No	No	Yes
Yes	Galea, 2022	Yes	Yes	Yes	Yes	No	Yes
Yes	Grandjean, 2011	No	Yes	Yes	Yes	No	No information
Yes	Grandjean, 2015	No	Yes	Yes	Yes	No	Yes
Yes	Marin, 2017	No	No information	Yes	Yes	No	No information
Yes	Martinson, 2022	No	Yes	Yes	Yes	Yes for diabetes	No
Yes	Restrepo, 2018	Yes	No information	Yes	Yes	Yes for diabetes	Yes
Yes	Shivakumar, 2018	Yes	Yes	Yes	Yes	Yes for diabetes	No
Yes	Shu, 2017	No	No information	No information	Yes	No	No information
Yes	Verrall, 2020	No	Yes	Yes	Yes	Yes for diabetes	Yes
Yes	Vo, 2023	No	No information	No	Yes	No	No information
No	Abdulkareem, 2020	No	No information	No information	Yes	No information	No
No	Allen, 2021	No	No information	yes	No	No	No information
No	Balcells, 2017	No	No information	Yes	Yes	No	Yes
No	Calderon, 2019	Yes	No	Yes	Yes	Yes for diabetes	No
No	Guo, 2022	Yes	Yes	Yes	Yes	Yes	Yes
No	Kaul, 2022	No	No information	yes	yes	No	No information
No	Kubiak, 2019	No	No information	Yes	Yes	Yes for diabetes	No information

No	Kyaw, 2019	No	No information	Yes	Yes	No	No information
No	Lebina, 2016	No	Yes	No	Yes	Yes for diabetes	Yes
No	Narasimhan, 2017	No	No	No	Yes	No	No
No	Oo, 2020	No	Yes	No	Yes	No	No information
No	Rajan, 2017	No	Yes	Yes	No	No	Yes
No	Sharma, 2022	No	No information	Yes	Yes	No	No information
No	Smith, 2022	Yes	No information	Yes	Yes	Yes	Yes
No	Suggaravetsirim, 2013	No	Yes	Yes	Yes	No	Yes
No	Velayutham, 2020	No	Yes	No	Yes	No	Yes
No	Velen, 2020	No	No information	Yes	Yes	No	No information
No	Zayar, 2020	Yes	Yes	Yes	Yes	Yes for diabetes	Yes

Table 5-5.Characteristics of studies without individual participant data

Study	Country	N	Age	% Female	Definition of household contacts	Diabetes	Other NCD
Abdulkareem, 2020	Iraq	521	Mean: 26.5	52.2%	Individuals who have had prolonged, frequent, or intense contact with infectious TB patients	Not defined	Not reported
Allen, 2021	Peru	129	Mean: 27	57.4%	Not defined	Not defined	Not reported
Balcells, 2017	Chile	144	Median: 37	55.6%	Resided in the household for at least 7 consecutive days during the 3 months prior to the diagnosis of TB in the index case	Not defined	Not reported
Calderon, 2019	Peru	138	NA	58.8%	Shared at least household where they sleep or take their meals (at least one of them per day).	2-h glucose ≥200 mg/dL (OGTT), HbA1c ≥ 6.5% or fasting plasma glucose ≥126 mg/dL.) OGTT only in individuals without prior DM diagnosis	Hypertension (BP measurement) and renal disease (not defined)
Guo, 2022	China	972	Mean: 46.6	57.2%	Lived in the same house with an index TB patient for more than 6 hours per week between 3 months earlier than the diagnosis of the TB index case and 14 days after the TB index case initiating anti-tuberculosis treatment.	Fasting plasma glucose ≥ 126 mg/dl, random plasma glucose ≥ 200 mg/dl or a previous diagnosis of DM	Hypertension (BP measurement and history of known disease)
Kaul, 2022	India	80	Median: 29	47.5%	Close contact of more than or equal to 8 h/day for at least 3 months, with the respective index TB patient after onset of the infection.	Not defined	Not reported
Kubiak, 2019	India	1113	Mean: 36.8	64.8%	Lived with the TB patient for at least the previous 3 months	RBG ≥200 mg/dL or self-report of a prior clinical diagnosis of diabetes	Renal failure (self-report)
Kyaw, 2019	Myanmar	620	< 5 yrs: 6.5% 5-14 yrs: 15.8% 15-49 yrs: 54.4% 49 yrs: 22.1%	58.4%	A person who shares the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the treatment or during the three months before the commencement of the current treatment	Self-report	Not reported

Lebina, 2016	South Africa	2464	Median reported by group*: 27; 23 ; 10	58.3%	Slept in that house >2 nights a week or ate > 4 meals a week or shared a living space for a cumulative 8 hours per week	Random blood glucose ≥ 10mmol/l. Unclear if contacts were systematically tested.	Not reported
Narasimhan, 2017	India	359	1–4 yrs: 7.3% 5–14 yrs: 20.7% 15–24 yrs: 21.2% 25–40 yrs: 28.5% 41–64: 18.7% ≥ 65 yrs: 3.6%	55.4%	An individual who has lived in the same house as a person with TB for a continuous period of 3 months.	Not defined	Not reported
Oo, 2020	Thailand	174	NA	67.8%	A person who shared the same enclosed living space for one or more nights or frequent or extended periods during the day with an index TB case during the 3 months before the commencement of the current treatment episode	Reviewing medical record	Not reported
Rajan, 2017	Brazil	1383	>18yrs: 50%	51.1%	No information	Self-report	Not reported
Sharma, 2022	India	536	Median: 40	55.8%	WHO definition: A person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment	Not defined	Renal disease (not defined)
Smith, 2022	Ethiopia	597	Median: 28.5 yrs	59.8%	(1) Persons who shared the same home residence as the index case for ≥5 nights during the 30 days prior to the date of TB diagnosis in the index case; or (2) persons who shared the same indoor living or working space as the index case ≥5 hours per day for ≥5 days during the 30 days prior to the index case’ s TB diagnosis.	Point-of-care capillary HbA1c ≥ 6.5% or self-report	Not reported
Suggaravetsiri, 2013	Thailand	1200	Mean: 32.8 yrs	56.2%	Person sharing the same kitchen and sleeping in the same house as the index	Self-report	Not reported

					TB case for an average of > 4 nights/week for at least 1 month.		
Velayutham, 2020	India	2150	Median: 30 yrs	59.7%	A person living with and sharing food from the same kitchen as the index patient for a minimum of three months prior to diagnosis of TB disease of the index case	Self-report	Not reported
Velen, 2020	Viet Nam	1254	Median 39 yrs in contacts with TB and 32 yrs in those without TB	56.4%	A person of any age living in the same household as the source case in the last 2 months at the time of participation in the ACT2 trial.	Self-report	Not reported
Zayar, 2020	Myanmar	328	NA	NA	Family members living in the same households with an index TB patient for at least 3 months before having a diagnosis of TB	Known DM or newly diagnosed DM with RBG ≥ 200 mg/dl and FBG ≥ 126 mg/dl (or) RBG ≥ 200 mg/dl for two times on separate days (or) FBG ≥ 126 mg/dl for two times on separate days	Not reported

*Sputum smear and culture screened, sputum Xpert MTB/Rif screened, and no sputum provided for testing

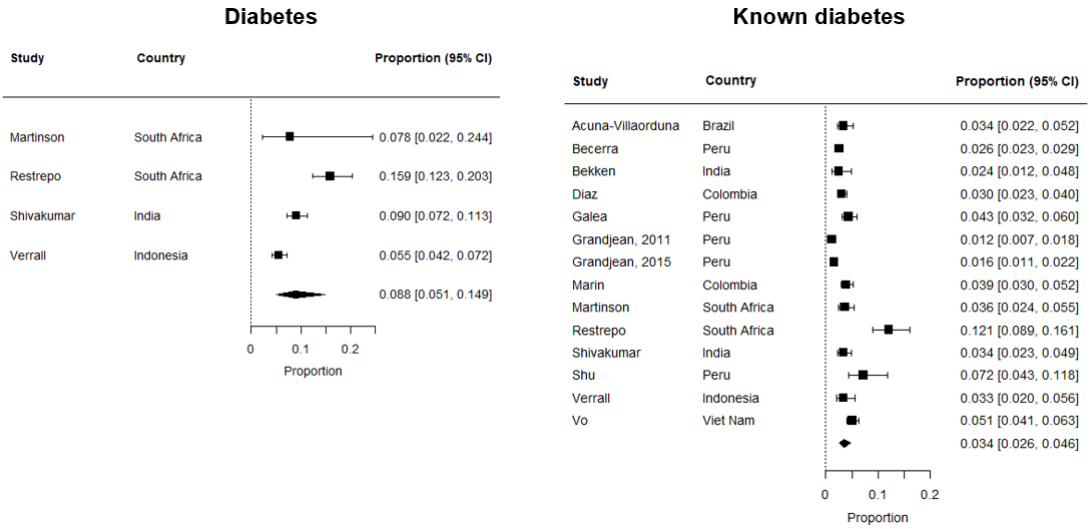
BP: blood pressure; TB: tuberculosis; RBG: random blood glucose; DM: diabetes

5.4.2. Prevalence of NCD

Based on 14 studies with data, the pooled prevalence of known diabetes was 3.0% (95% CI 2.3-4.1%) (Figure 5-3). The prevalence ranged from 1.2% in a study in Peru [206] to 12.1% in a study in South Africa.[141] There was no evidence that the prevalence varies by region (p = 0.061) (Figure 5-4).

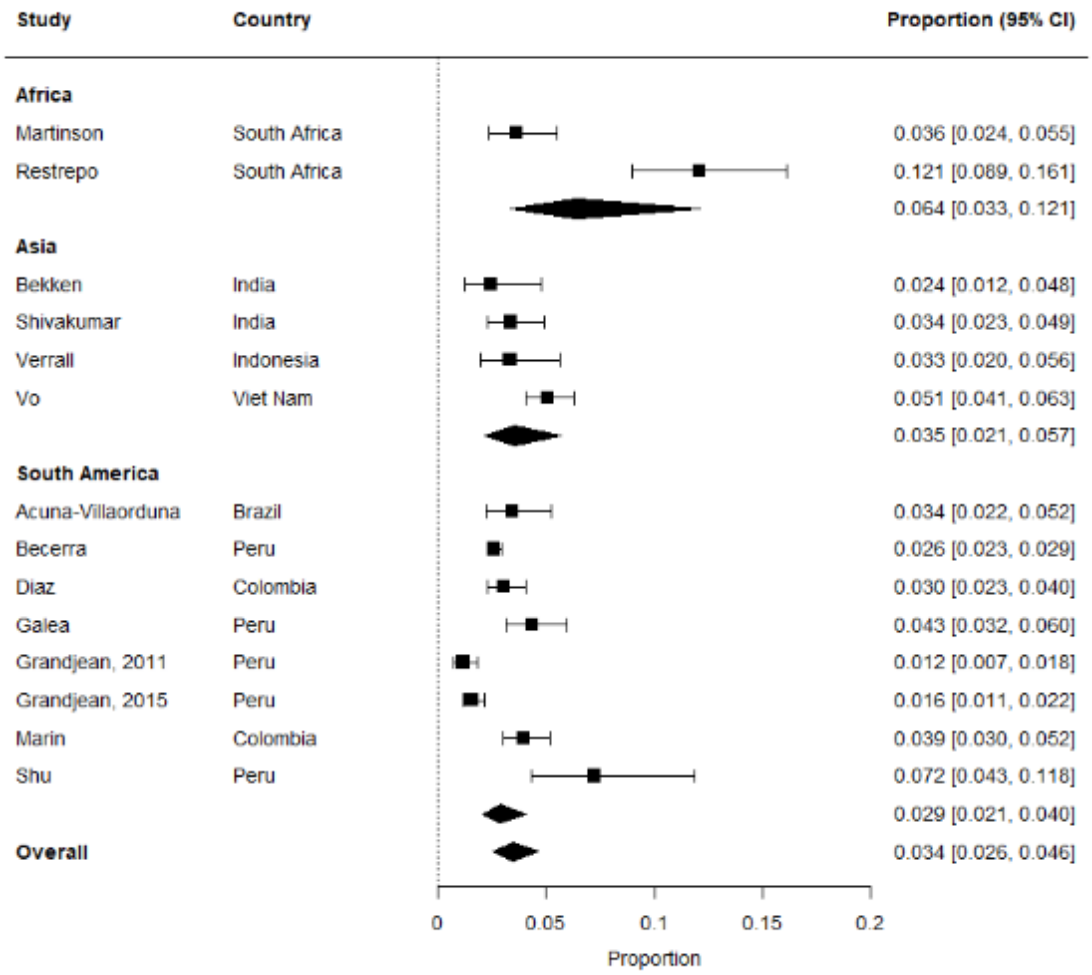
Four studies used blood tests to identify previously undiagnosed diabetes in addition to known diabetes. The pooled prevalence of diabetes (including known and newly identified diabetes) was 8.8% (95%CI, 5.1-14.9%, (Figure 5-3).

Figure 5-3.Prevalence of diabetes and known diabetes



Estimates are based on the pooling of 20 imputed datasets. The denominators and numerators vary across the imputed datasets, and thus are not presented.
Diabetes: I-squared=90.4% (95%CI 78.4-95.7), p = <0.0001, tau2 = 0.26
Known diabetes: I-squared=91.5% (95%CI 87.5-94.2), p = <0.0001, tau2 = 0.33

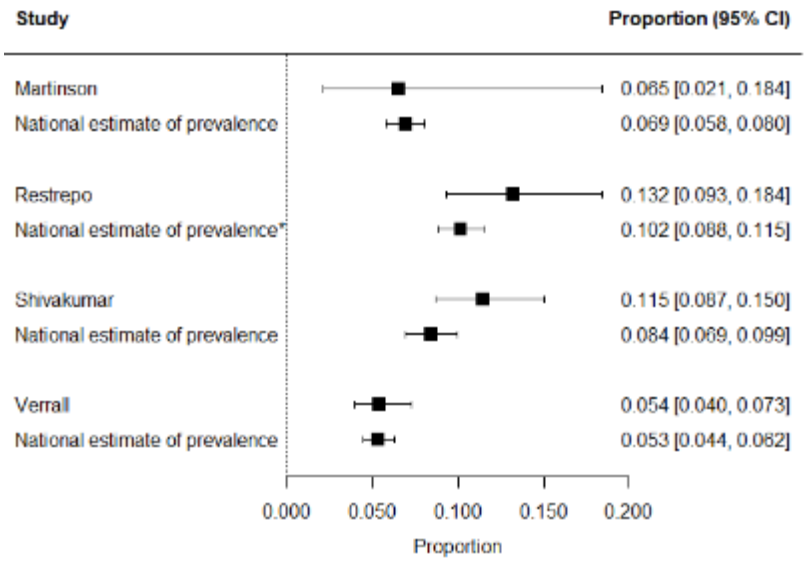
Figure 5-4.Prevalence of known diabetes by region



P-value from the likelihood ratio test comparing a model with and without region = 0. 061

The age-sex standardised prevalence of diabetes ranged from 5.4 to 11.5% (Figure 5-5), and their point estimates were higher than the standardised national prevalence estimates in two studies, in South Africa (10.4%, 95% CI 6.8-15.5% vs 6.9%, 95%CI 5.8-8.0%)[141] and India (11.5%, 95% CI 8.7-15.0% vs 8.4%, 95% CI 6.9-9.9%).[209]Another study in South Africa had a large confidence interval due to missing data[214], and in a study in Indonesia, the estimate was similar to the national estimate (5.4%, 95% CI 4.0-7.3% vs 5.3%, 95% CI 4.4-6.2%).[213]

Figure 5-5.Age-sex-standardised prevalence of diabetes and the national standardised estimates



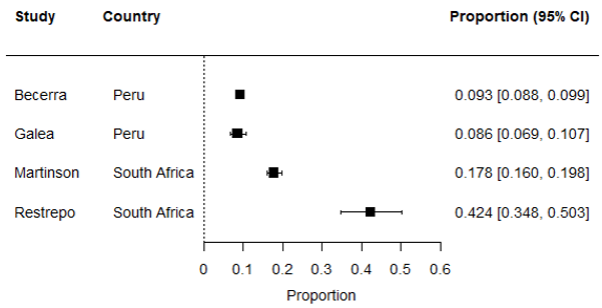
GBD: Global Burden of Disease; CI: confidence interval

National estimates of prevalence are based on the 2019 Global Burden of Disease estimates**.** Both study and national estimates are standardised for age and sex using 2019 national population estimates.

Data on other NCD were limited (Figures 5-6, 5-7, and 5-8). Hypertension was reported in four studies. The prevalence ranged from 8.6% (95% CI 6.9-10.7%) in a study in Peru to 42.4% (95%CI, 34.8-50.3%) in a study in South Africa (Figure 5-6). Due to this large heterogeneity, I did not meta-analyse the prevalence estimates. The pooled prevalence of renal and cardiovascular disease was 1.0% (95% CI 0.4-2.7%) and 1.6% (95% CI 0.7-3.5%), respectively

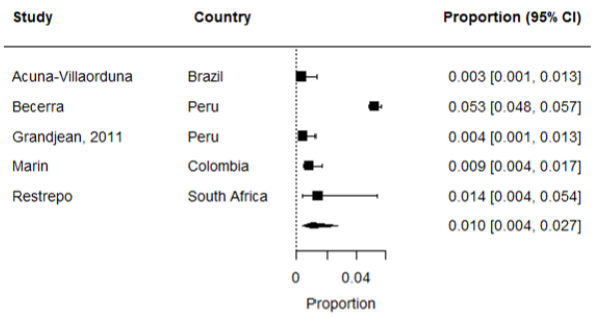
(Figures 5-7 and 5-8). Based on one study, the prevalence of depression was 22.0% (95%CI 19.3-24.8%).[212]

Figure 5-6.Prevalence of hypertension among household contacts



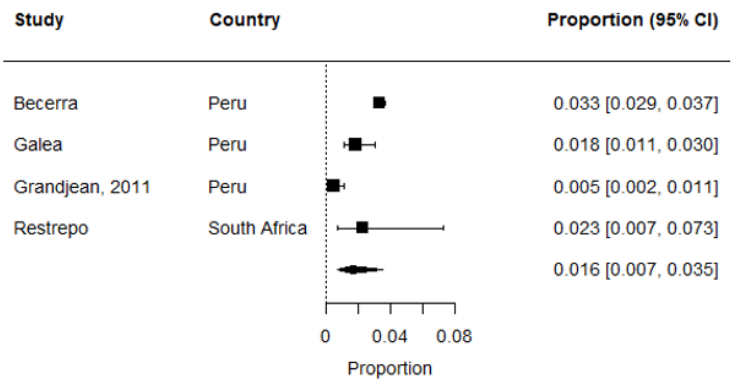
I-squared=98.7% (95%CI 98-99.2), p = <0.0001, tau2 = 0.88

Figure 5-7.Prevalence of renal disease among household contacts



I-squared=94.1% (95%CI 89.1-96.8), p = <0.0001, tau2 = 1.21

Figure 5-8.Prevalence of heart disease among household contacts



I-squared=88% (95%CI 71.7-94.9), p = <0.0001, tau2 = 0.62

The prevalence estimates accounting for clustering within households are presented in Table 5-6.

Table 5-6.Prevalence of NCDs, accounting for clustering within households

NCD	Prevalence, % (95% CI)	Heterogeneity statistics
Known diabetes	3.0 (2.3-4.1)	I^2 =83.2% (95%CI 71.3-90.1), p ≤ 0.001, tau2 = 0.2
Diabetes	7.3 (3.9-13.4)	I^2 = 73.2% (95%CI 10-92), p = 0.024, tau^2 = 0.09
Hypertension	35.1 (33.0-37.3)	I^2 = 99.7% (95%CI 99.6-99.8), p ≤ 0.001, tau2 = 0.99
Renal disease	1.0 (0.3-3.5)	I^2 = 95.3% (95%CI 91-97.6), p ≤ 0.001, tau2 = 1.57
Heart disease	1.5 (0.5-4.6)	I^2 = 91.8% (95%CI 79.3-96.8), p ≤ 0.001, tau2 = 0.9

NCD: non-communicable diseases; CI: confidence interval

The NCD prevalence did not differ significantly between contacts with and without TB (Table 5-7).

Table 5-7.Prevalence of NCD by TB status among contacts

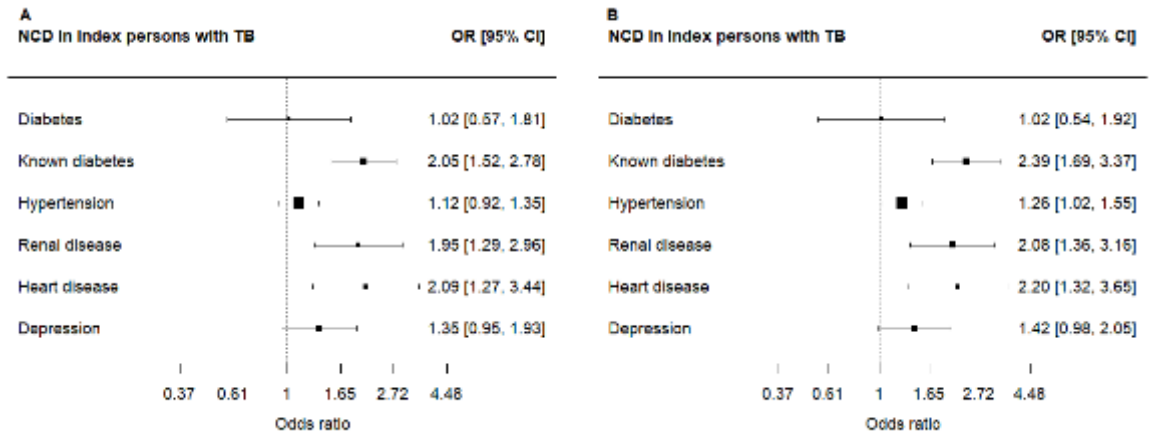
	% prevalence (95% CI)		
NCD	With TB	Without TB	OR (95% CI)
Known diabetes	3.4 (1.8-6.1)	3.5 (2.5-4.7)	1.09 (0.62-1.92, p=0.7632)
Diabetes	8.4 (2.7-22.9)	8.6 (5.8-12.4)	1.08 (0.38-3.08, p=0.8809)
Hypertension	13.6 (4.5-34.5)	16.5 (8.2-30.3)	0.89 (0.62-1.26, p=0.5020)
Renal disease	2.7 (0.5-11.9)	1.3 (0.5-3.6)	0.74 (0.37-1.49, p=0.3944)
Heart disease	5.3 (3-9.3)	3.2 (2.9-3.6)	1.67 (0.9-3.1, p=0.1057)

NCD: non-communicable diseases; CI: confidence interval

5.4.3. *Association between NCD in index people with TB and NCD in contacts*

When adjusted for age and sex of index people with TB, diabetes in index people with TB was not significantly associated with the presence of diabetes in contacts (OR 0.84, 95% CI 0.51-1.40, p=0.9523) (Figure 5-9). In contrast, known diabetes, renal disease, and cardiovascular disease in people with TB were associated with the presence of the same NCD in contacts (for known diabetes, OR 2.05, 95%CI 1.52-2.78 p< 0.0001). The associations remained when additionally adjusting for the age and sex of contacts (Figure 5-9). Depression had a similar association, although not significant (OR 1.42, 95% CI 0.98-2.05, p=0.0605).

Figure 5-9.Associations between NCD in index people with TB and NCD in contacts



A. Odds ratios were adjusted for age and sex of index people with TB.
B. Odds ratios were adjusted for age and sex of both index people with TB and household contacts.

TB: tuberculosis; OR: odds ratio; CI: confidence interval
The odds ratios indicate the association between NCD in index people with TB and the same NCD in contacts (i.e. clustering of NCD).

5.4.4. Sensitivity analysis

The prevalence of NCD was similar in a sensitivity analysis that applied multiple imputation ignoring households and another that excluded studies with missing data on outcomes in > 50% of contacts (Table 5-8).

Table 5-8.Prevalence of NCD-sensitivity analysis

	% prevalence (95% confidence interval)		
NCD	Sensitivity analysis		Original imputation model
	Imputation model ignoring household clustering*	Excluding studies with large missing data**	
Known diabetes	3.5 (2.5-4.7)	3.4 (2.4-4.8)	3.4 (2.6-4.6)
Diabetes	8.6 (5.9-12.5)	9.2 (5.6-14.9)	8.8 (5.1-14.9)
Renal disease	1.3 (0.5-3.6)	0.9 (0.3-3)	1.0 (0.4-2.7)
Heart disease	1.7 (0.8-3.5)	1.5 (0.6-3.7)	1.6 (0.7-3.5)

NCD: non-communicable diseases
*I used imputation models ignoring households regardless of the availability of household identifiers, while the original imputation assigned the same household identifiers to studies without data on index people with TB.

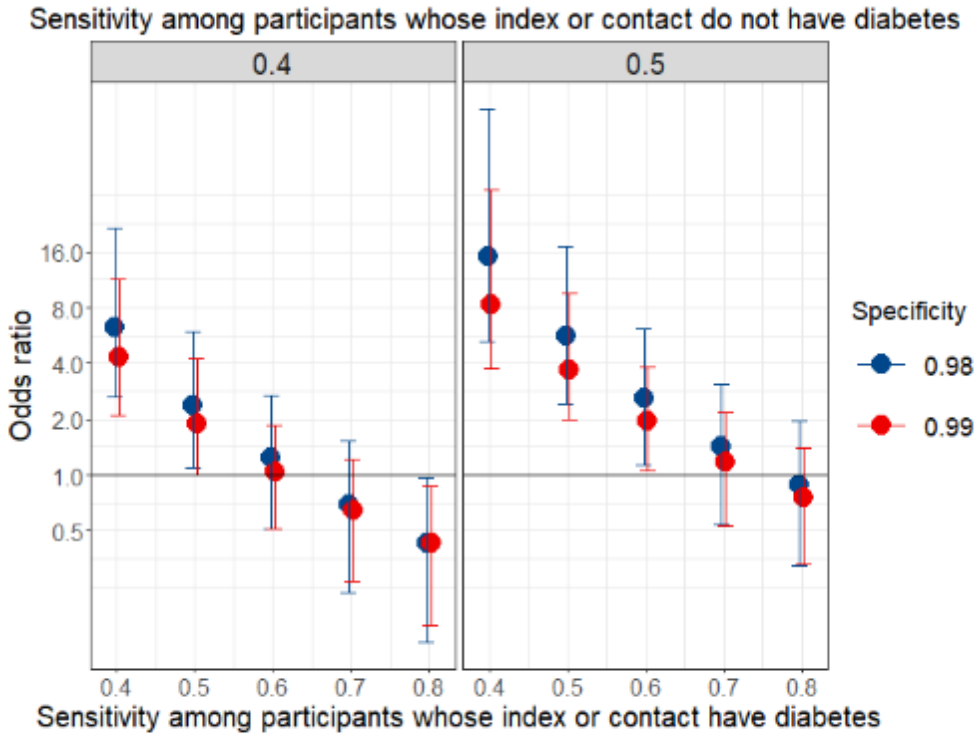
** Excluded studies with missing data on outcomes in > 50% of contacts.

For hypertension, the primary analysis did not perform a meta-analysis due to heterogeneity.

The quantitative bias analysis indicates that the observed association might be explained by differential misclassification of diabetes status (Figure 5-10). For

example, when I assume a sensitivity of self-reported diabetes at 60% for individuals living with a household member diagnosed with diabetes, compared to 40% in those without any household member with diagnosed diabetes, the confidence interval for the true association overlapped with null.

Figure 5-10.Impact of the misclassification on the association between self-reported diabetes in index people with TB and their contacts



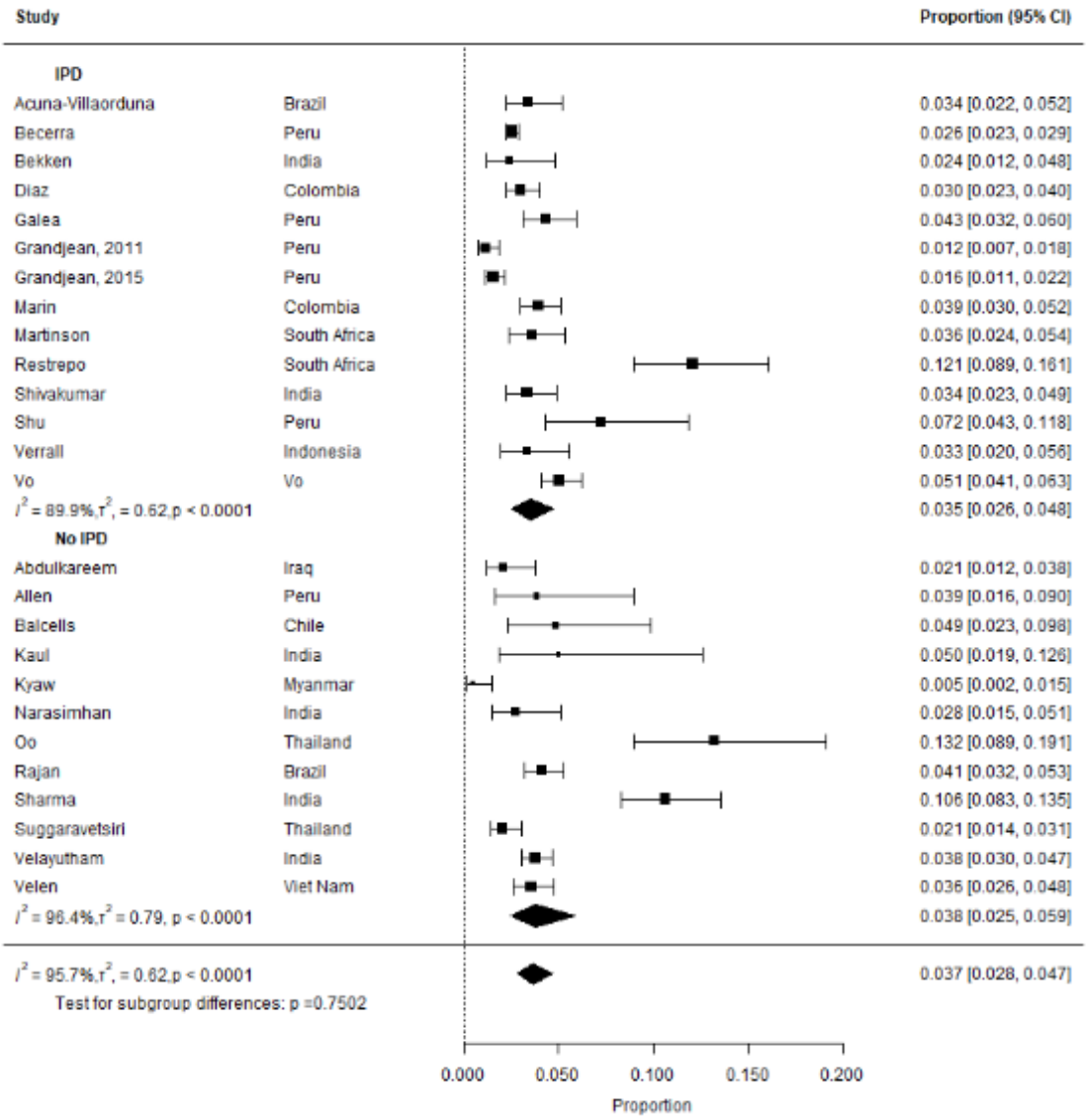
Odds ratios are adjusted for age and gender of index people with TB and contacts.
Odds ratios in the analysis using original diabetic status: OR 2.25 (1.56-3.25).

5.4.5. Meta-analysis of aggregated data

The prevalence of NCD did not differ significantly by the availability of IPD (Figures 5-11, 5-12, 5-13, and 5-14). The funnel plot did not show evidence of publication bias (Test for Funnel Plot Asymmetry: z = -1.1122, p = 0.2661, Figure 5-15).

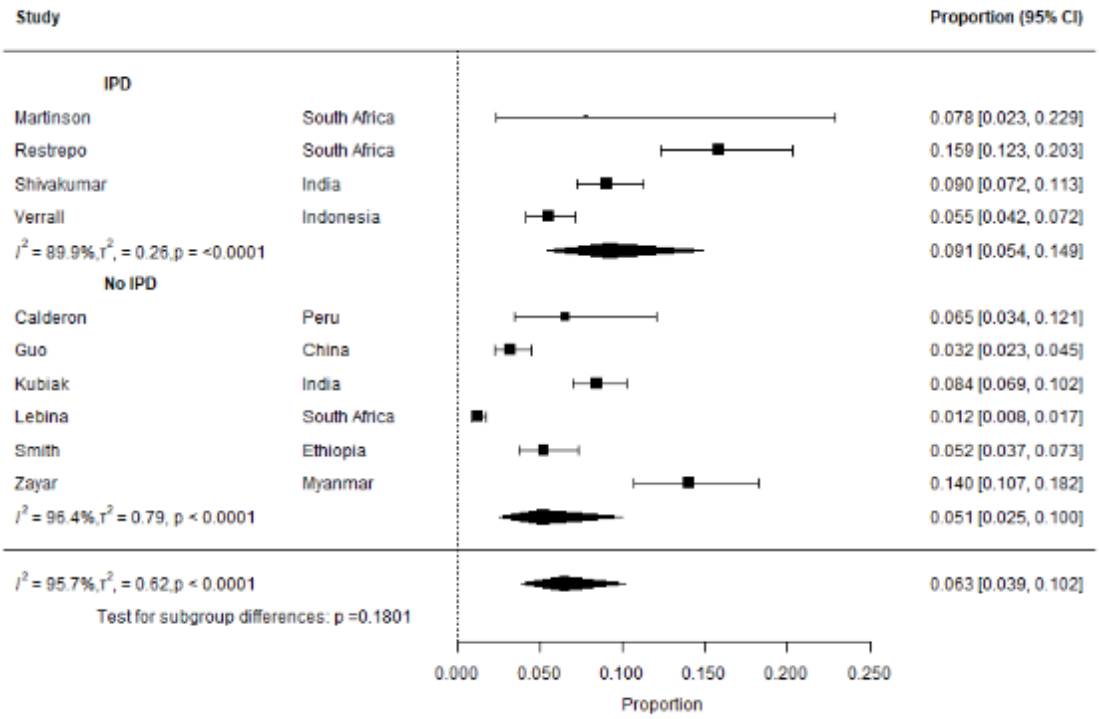
Two studies without IPD reported the prevalence of self-reported diabetes in a control group.[220,229] In one study in India, the prevalence of self-reported diabetes among household contacts was 2.8% (10/359) compared to 4.7% (17/361) in individuals in the same community (prevalence ratio 0.59, 95% CI 0.27-1.27).[220] In another study in Chile, the prevalence was 4.9% (7/144) vs 3.2% (1/31) (prevalence ratio 1.51, 95% CI 0.19-11.81) when compared to healthy volunteers.[229]

Figure 5-11.Prevalence of known diabetes including studies with and without IPD data



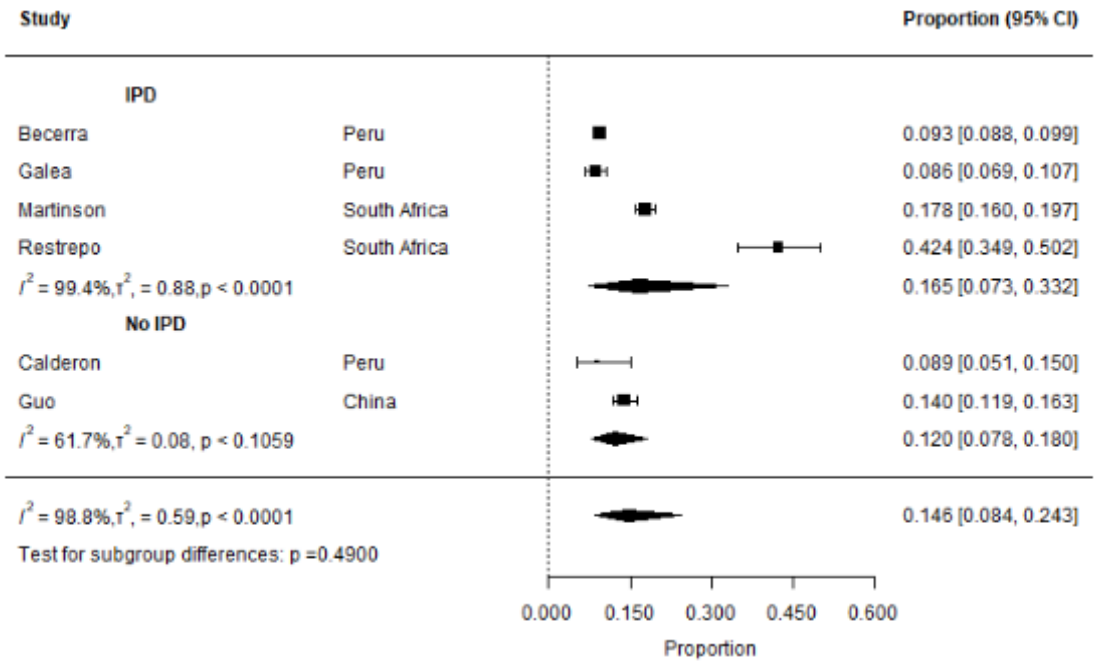
IPD: individual participant data; CI: confidence interval

Figure 5-12.Prevalence of diabetes including studies with and without IPD



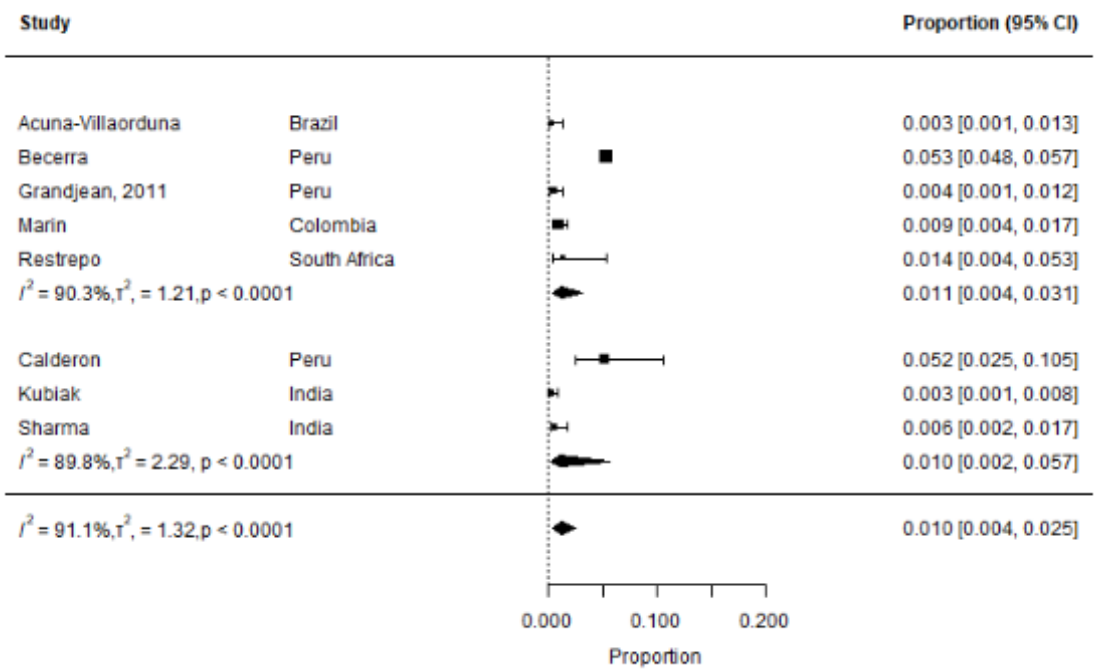
IPD: individual participant data; CI: confidence interval

Figure 5-13.Prevalence of hypertension including studies with and without IPD



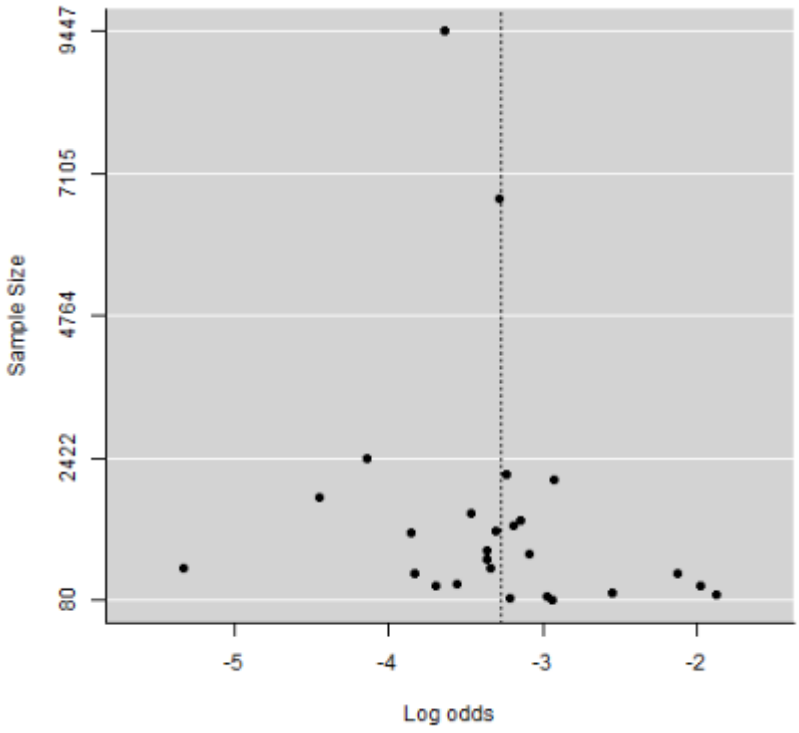
IPD: individual participant data; CI: confidence interval

Figure 5-14.Prevalence of renal disease including studies with and without IPD



IPD: individual participant data; CI: confidence interval

Figure 5-15.Funnel plot of studies reporting the prevalence of known diabetes



Test for Funnel Plot Asymmetry: z = -1.1122, p = 0.2661

5.5. Discussion

This study systematically evaluated the prevalence of NCD among contacts of people with TB. I found a small number of studies using standard ascertainment of diabetes, making it difficult to understand its actual burden. In two of four studies that used blood tests, age and sex-standardised prevalence of diabetes among contacts tended to be higher than the corresponding national estimates. However, it is inconclusive because of an indirect comparison and wide confidence intervals. Only two studies allowed a direct comparison of diabetes prevalence but with data based on self-report and small sample sizes. Additionally, data on other NCD were limited, and when reported, the diagnoses were either not based on standard tests or were unclear.

There has been a global push for the integrated screening and management of TB and its comorbidities, notably diabetes.[11,131] Despite this, policy adoption and implementation remain suboptimal. Recent data reveals that only 15 of the 30 countries with high TB burden have recommended TB screening for people with diabetes in their guidelines, and programmatic data on the implementation are lacking.[188] Contact investigation is a critical component of TB programmes, serving as a gateway for TB preventive treatment and improved TB detection. Leveraging this for NCD screening benefits people with TB as well as their families, promoting a holistic approach. Such a household-wide integration can address multiple diseases that are risk factors for TB and, if left unmanaged, can deteriorate both TB and NCD outcomes.

In my study, the prevalence of known diabetes, based mostly on self-report, was lower than that of diabetes, including both known diabetes and diabetes newly identified through blood tests (3.4% vs 8.8). This discrepancy is consistent with studies reporting a low sensitivity of self-reported diabetes.[147,148] The gap indicates the underdiagnosis of diabetes among contacts of people with TB. Screening and subsequent management of diabetes might help address the gaps and reduce the risk of TB. Likewise, the prevalence of other NCD was much lower than the national estimates, most likely due to the

reliance on the self-report. The underreporting might be more prevalent in individuals from the lowest socio-economic strata, as is usually the case for people with TB and their families.[233]

This review suggested that contacts were more likely to have known diabetes and other NCD that mainly were self-reported when their index people with TB had the same NCD. This may be because household members share similar access to health care, leading to a higher chance of being diagnosed with NCD, rather than the actual increase in the prevalence. My sensitivity analysis also suggested that the association could be explained by differences in the extent of underdiagnosis. Household contact tracing could be an excellent opportunity to screen for diabetes among household members who otherwise do not have access to care. For diabetes based on laboratory tests, there was no association with diabetes among index people with TB. However, since the confidence interval was wide, the clustering of diabetes and other NCD in households affected by TB cannot be excluded yet.

A limitation of this review was the small proportion (38%) of eligible studies that provided IPD. Challenges in data retrieval are common, especially when including non-randomised studies.[234] Low data retrieval rates may result in bias. I mitigated this risk by conducting a meta-analysis using aggregate data, which did not suggest a substantial difference in the estimates by the availability of datasets. Another area for improvement is the need for more studies using standard NCD diagnostic methods (e.g.HbA1c for diabetes) among household contacts.

5.6. Conclusion

This systematic review and meta-analysis showed a high prevalence of diabetes among contacts, compared to a low prevalence of known diabetes, highlighting a gap in the diagnosis. This suggests a need for integrated screening and management targeted to households affected by TB. It, however, remains inconclusive whether contacts have a higher prevalence of diabetes

than the general population. Future studies should address this knowledge gap by applying systematic diabetes screening with a control group from the same geographic areas. Furthermore, prospective household control studies using standard diagnostic methods are needed to address limited data on other NCD.

6. The clinical pattern of multimorbidity among household contacts of people diagnosed with TB compared to control households

6.1. Abstract

Background:

Integration of NCD screening and care within TB households could help address the dual epidemics TB and NCD. Limited data exist on the NCD prevalence among household contacts compared with individuals in the same neighbourhood.

Method:

I conducted a pilot cross-sectional clinical study in South Africa and Tanzania, enrolling adults living in households with a known person with TB (contacts) and those in neighbourhood households (controls). The study was nested within a contact investigation project (CUT-TB). I planned to enrol 100 households of index TB patients and 100 neighbourhood households in each country to achieve 80% power to detect at least a 33% higher prevalence of at least one NCD in household contacts compared to controls. However, operational challenges resulted in a smaller sample size. I systematically measured blood pressure and tested for spot blood glucose, HbA1c, serum creatinine, and total cholesterol. Total cholesterol was used to estimate 10-year CVD risk using the WHO risk chart.

Results:

I enrolled 203 adult contacts of 121 persons with TB and 160 controls. Among contacts, the prevalence of diabetes, hypertension, and chronic kidney disease were, 12.2% (95%CI 8.3-17.6%), 39.2% (95% CI 32.6-46.2%), and 10.0% (6.5-15.2%), respective, compared to 14.1% (95% CI 9.2-21.0%) and 44.7% (95% CI 36.9-52.7%), and 8.9% (95% CI 5.3-14.5%) among controls. At least one NCD was present in 48.9% (95% CI 41.9-56%) vs 51.9% (95% CI 43.8-60%) in each group. More than half of NCDs were newly identified. Among contacts and

controls, 3.2% (95% CI 1.4-7.0%) and 4.0% (95% CI 1.8-8.5%), respectively, had a > 20% 10-year CVD risk.

Conclusions

I found a high prevalence of undiagnosed NCD among contacts and neighbourhood controls. This suggests a potential benefit of integrating NCD screening and care with contact investigations. Such an integrated approach could be extended to the wider community, not only among TB household contacts where TB burden is high.

6.2. Introduction

My systematic review of TB prevalence surveys did not show the difference in NCD prevalence between members of households with and without TB (Chapter 3). However, prevalence surveys used participants' self-report to ascertain NCD. The prevalence of NCD was much lower than expected from the national statistics in all groups, suggesting that underreporting is likely. Furthermore, prevalence surveys had limited data on NCD, nine surveys for diabetes and only two for hypertension, both of these were inconsistently assessed, and none for other NCD such as dyslipidemia and chronic kidney disease.

Another review (Chapter 5) found a few contact tracing studies that explored the prevalence of NCDs, mainly diabetes, among household contacts. However, these studies lacked control groups, limiting their ability to provide comparative data.[141,209,221,224] In the absence of a control group, understanding the comparative prevalence of NCDs in contacts is challenging. A comparison with national prevalence provides limited insights as NCD prevalence can vary regionally, and demographics may differ between household contacts and the general population. Further, data on other NCD, such as hypertension and CKD were limited.

As summarized in section 1.7, WHO recommends opportunistic screening for hypertension in adults, with an emphasis on people with CVD risk factors, and screening for diabetes in asymptomatic individuals aged over 40 years who are at least overweight (i.e., BMI >25). South Africa has similar recommendations, advocating opportunistic hypertension screening in adults attending primary care facilities, supplemented by screening conducted by community health workers.[235] For diabetes, it recommends screening in adults who are overweight and have at least one risk factor (e.g., physical inactivity, dyslipidemia) or those who are aged ≥45 years without risk factors.[236] In light of this, the 2022-2027 national strategic plan for the prevention and control of NCD proposes a target of 90% of all people over 18 knowing their diabetes and hypertension status.[237]

However, data on the gap in the diagnosis of diabetes and hypertension among household contacts are lacking. Furthermore, although hypertension, CKD, and dyslipidemia are also important conditions guiding the management of CVD risk alongside diabetes, data on their prevalence among household contacts are lacking.

6.3. Method

6.3.1. Study aim Objectives

Aim

Derive evidence to inform the design of multifaceted clinical and socio-economic interventions for TB and key NCD multimorbidity in households affected by TB and in the community.

Objective

1) To describe and compare the prevalence of key NCD multimorbidity among household contacts of people with TB and members of neighbourhood households.
2) To determine the yield of systematic integrated screening for TB infection, NCD and related risk factors compared to control households.
3) To assess the costs and cost-effectivness of integrating NCD screening within household contact investigations (Chapter 7).

6.3.2. Study design

Design

A cross-sectional clinical study comprising two parts: 1) screening of multimorbidity in household contacts of TB patients and 2) screening the same conditions in members of the neighbourhood households (Figure 6.1).

The clinical study was embedded in an ongoing study to evaluate the effectiveness of universal testing for TB to increase the number of TB cases identified among household contacts of TB patients (Community and Universal

Testing for TB among contacts: CUT-TB).[238] The project was conducted in three countries, South Africa, Tanzania, and Lesotho, in two consecutive phases.

During phase 1, household contacts of 100 TB patients in each country were enrolled to evaluate the prevalence of TB infection. This pilot clinical study was nested within phase 1 of the CUT-TB study and was conducted in Ekurhuleni in South Africa and Mbeya region in Tanzania. The study assessed the prevalence of NCDs among household contacts of people with TB compared to individuals in the same neighbourhood (control group).

Setting

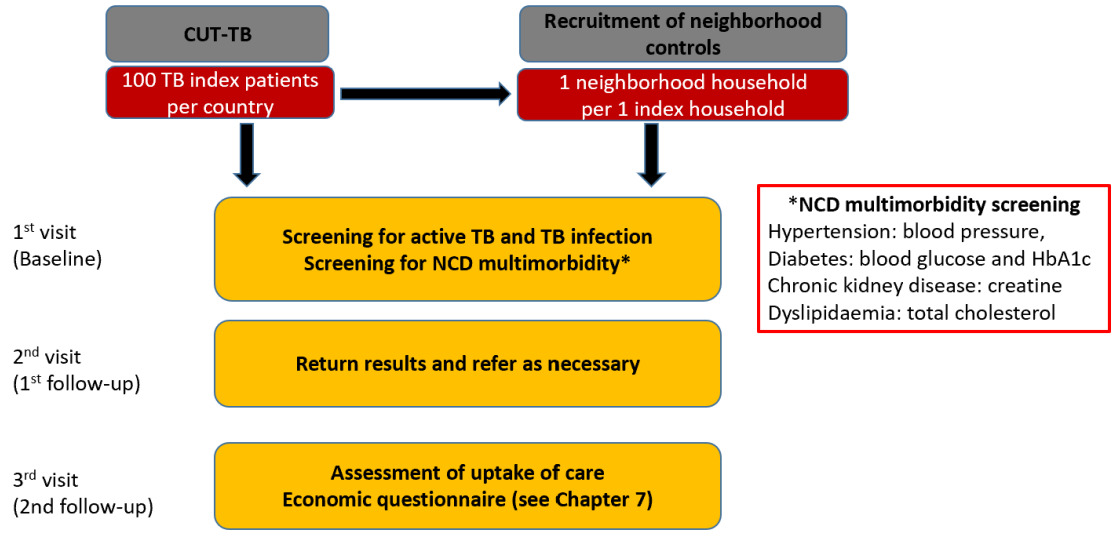
Annual TB notification rates in Ekurhuleni and Mbeya region are around 300 and 150 cases per 100,000 populations, respectively.[239,240] There is a lack of data on the NCD prevalence in Ekurhuleni. In Gauteng, where Ekurhuleni is located, the Demographic and Health Survey (DHS) in 2016 reported a hypertension prevalence of 42.3% in women and 39.5% in men and a diabetes prevalence of 9.3% in women and 6.6% in men.[241] In the Mbeya region, the DHS in 2022 reported a hypertension prevalence of 6.4% in women and 9.7% in men, but no data are available for diabetes.[242]

Recruitment

During Phase 1 of CUT-TB, I consecutively enrolled index patients diagnosed with bacteriologically confirmed drug-sensitive or drug-resistant TB of all ages who do not live alone from clinics in the study sites. After obtaining consent, my field team visited their households to enrol adult household contacts (≥18 years). For controls, I enrolled one neighbourhood household per TB patient, and their adult household members were invited. In South Africa, I generated random coordinates using an R package “sf” to identify households within the same ward as the TB patients (see Appendix 2 for detailed procedures).[243] Wards are a sub-division of municipalities used for the election. There are 112 wards in the city of Ekurhuleni, and their median area is 7.4 km^2 (interquartile range: 3.0-17.7). In Tanzania, I did the same in the city of Mbeya, but in the

other areas, due to operational challenges, I enrolled households closest to the index households. The field team visited these households, and after obtaining consent from the household heads, they invited their household members to participate in the study. If declined, the field team repeated the above process until at least one household per TB patient was enrolled.

Figure 6-1.Study schema



6.3.3. On-study procedures

I trained and supervised a field operation team, including research assistants and a nurse, for data collection. At baseline, the team collected sociodemographic information (e.g. age, gender, years of education, and employment status), risk factors such as smoking and alcohol use, and medical history through interviews. I additionally measured height, weight, and blood pressure. For blood pressure, two readings were performed, and the second reading was used. I tested for random blood glucose using serum samples in South Africa and capillary blood in Tanzania. I additionally tested for HbA1c, total cholesterol, and creatinine using venous blood in local laboratories. HIV counselling and testing was offered if their status was unknown for more than six months. All participants were asked to sign the consent form before HIV testing was done. In addition, a trained counsellor conducted HIV counselling before and after the HIV test in a private room.

The second household visit was arranged as soon as the results of the NCD screening were available. Participants received the results and, if deemed necessary as per pre-defined criteria, they were referred to nearby clinics. At the third household visit, information on subsequent referrals was collected.

6.3.4. Outcomes

Primary outcomes

The primary outcome was the presence of at least one of the NCDs below:

Diabetes mellitus: defined as HbA1c ≥ 6.5% or history of diagnosis.[121]

Hypertension: defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or history of diagnosis.[121]

Chronic kidney disease (CKD): defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min, which was calculated using the 2021 CKD Epidemiology Collaboration creatinine equation.[244,245]

Secondary outcomes

I investigated the prevalence of individual NCD separately as well as multimorbidity, defined as having two or more chronic conditions of NCDs and HIV (i.e. at least one NCD along with HIV or having two or more NCDs). Additionally, I calculated CVD risk over ten years using the WHO CVD lab-based risk chart (Figures 6-2 and 6-3). I then evaluated the prevalence of CVD risk > 20%, which requires statin therapy per the WHO guidelines.[246] The WHO CVD lab-based risk charts use a combination of age, sex, systolic blood pressure, smoking, diabetes, and total cholesterol to estimate the CVD risk over ten years. The risk prediction model was developed and validated by the WHO, using prospective multi-country cohorts.[246]

For ascertaining NCD, I did not require multiple measurements; hence, my investigation was meant for screening rather than confirmatory diagnosis. A

single measurement has been pragmatically used in other epidemiological studies evaluating NCD prevalence.[141,209,247]

Figure 6-2.World Health Organization cardiovascular disease risk laboratory based charts for Southern Sub-Saharan Africa

Reproduced from https://www.who.int/news/item/02-09-2019-who-updates-cardiovascular-risk-charts License: CC BY-NC-SA 3.0 IGO.

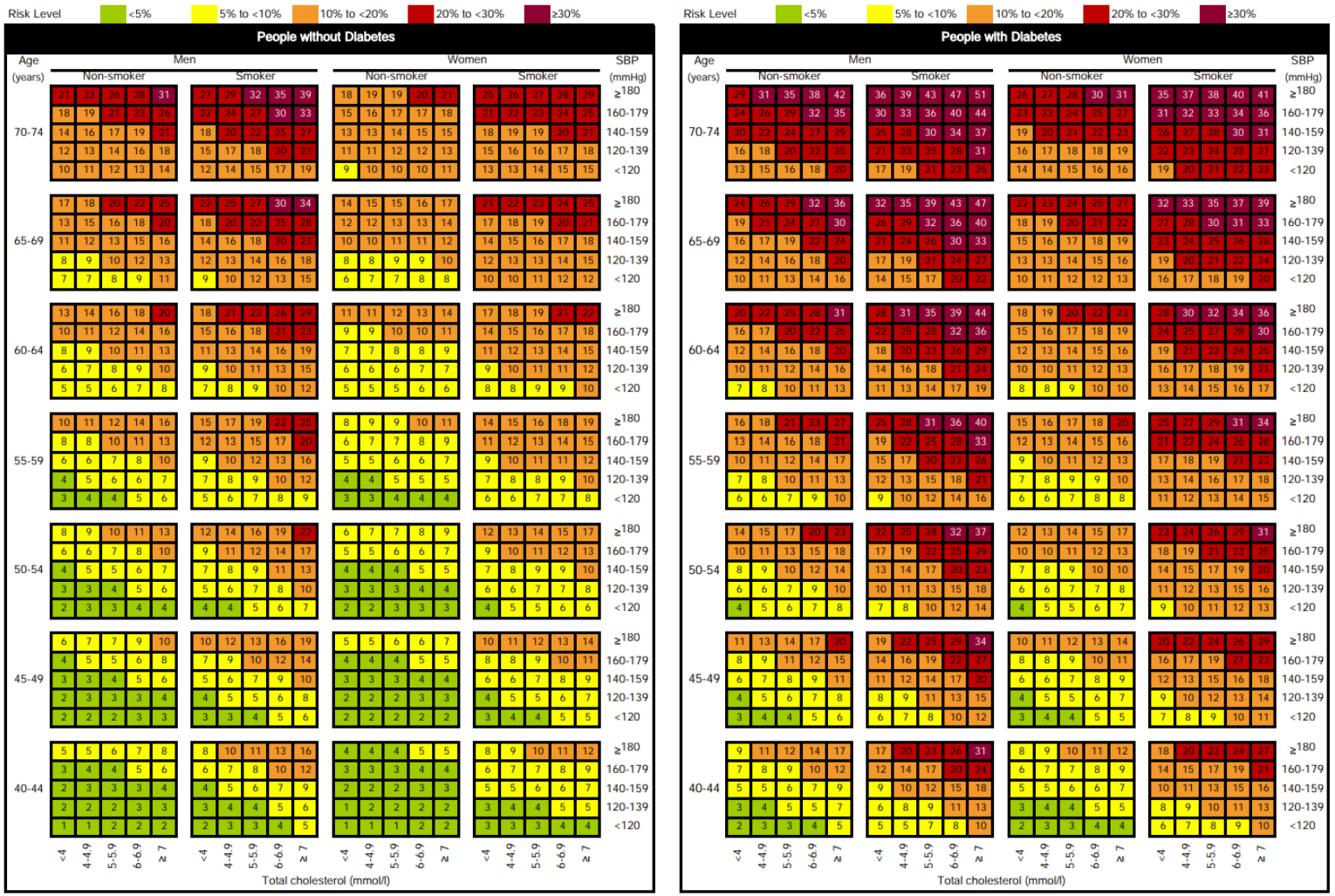
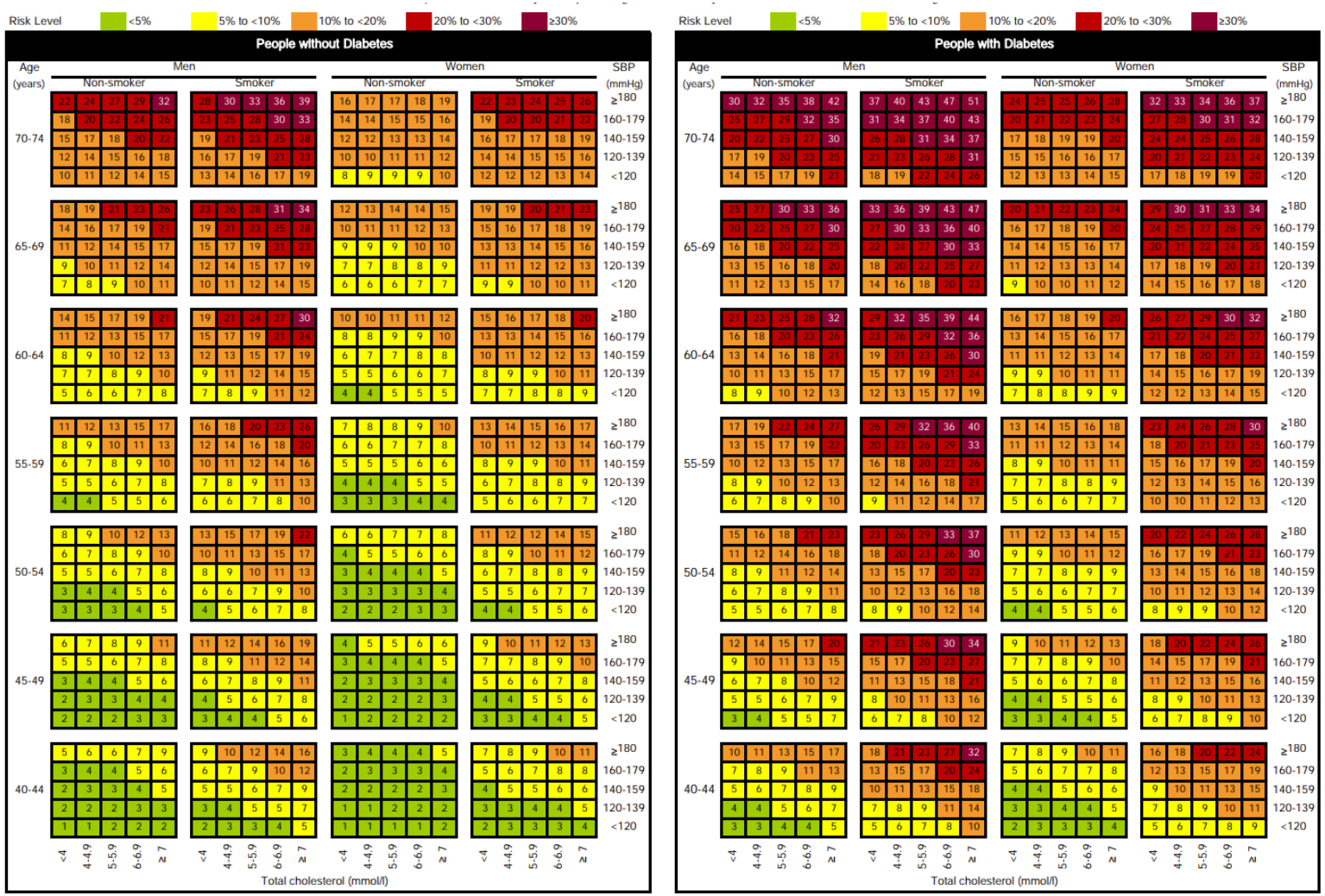


Figure 6-3.World Health Organization cardiovascular disease risk laboratory based charts for Eastern Sub-Saharan Africa
Reproduced from https://www.who.int/news/item/02-09-2019-who-updates-cardiovascular-risk-charts License: CC BY-NC-SA 3.0 IGO.



6.3.5. Sample size

I planned to enrol 100 households of index TB patients and 100 neighbourhood households in each country. I assumed 200 and 300 adult household contacts and 250 and 350 neighbourhood controls would be enrolled in South Africa and Tanzania, respectively. Based on existing literature, the prevalence of NCD was expected to range from 8% (e.g. diabetes) to 40% (hypertension). To estimate a margin of error, the effective sample size (ESS) was calculated as ESS = mk / DE, where m is the cluster sample size (i.e., number of contacts per index), k is the number of clusters (i.e., 100 index cases), and DE is the design effect, calculated assuming an intra-cluster correlation coefficient of 0.1. The total number of contacts is calculated using mk. The 95% CIs for an expected prevalence of NCD was estimated using the Clopper–Pearson method. The margins of error (± 95% CI) are presented in Table 6-1. Further, assuming that the prevalence of at least one NCD was 40% among neighbourhood controls, I used a normal approximation method to calculate a power to detect a difference in the prevalence,[248] ignoring the clustering since the association can be estimated within clusters. It was estimated that enrolling at least 200 household contacts and 250 neighbourhood controls would provide 80% power to detect at least 33% higher prevalence (i.e. the prevalence of 53.2% or higher) in household contacts at a 5% significance level.

Table 6-1.The margin of error by prevalence of NCD and number of contacts

	Prevalence					
	8%	15%	20%	30%	40%	50%
# of contacts	Margin of error (%)					
200	4.3	5.4	6	6.9	7.3	7.5
250	3.8	5	5.5	6.3	6.7	6.8
300	3.6	4.6	5.1	5.9	6.2	6.4
350	3.3	4.4	4.8	5.5	5.9	6

6.3.6. Statistical analysis

I presented the prevalence of NCD, multimorbidity, and CVD risk > 20% in household and neighbourhood contacts with robust 95% confidence intervals

acknowledging clustering within households. To calculate the prevalence, I excluded participants with missing NCD data.

To determine whether household contacts have a higher likelihood of NCD compared to neighbourhood controls of the same age and gender, I calculated the odds ratios for NCDs in contacts versus controls. This was achieved using logistic regression models fitted with a generalised estimating equation, accounting for clustering by index cases. The model adjusted for the pre-specified variables of age and gender. This analysis was conducted for the outcomes defined above. While I originally planned to conduct the analysis separately in each country, due to a small sample size from Tanzania, I merged the two populations. The model did not adjust for countries due to the small sample size in Tanzania.

I presented the pattern of multimorbidity visually using a Venn diagram.[249]

6.3.7. Ethical considerations

I obtained written informed consent from all study participants. Ethical approval was obtained from the Ethics Committee at the University of the Witwatersrand (210107), South Africa, the National Institute for Medical Research, United Republic of Tanzania (NIMR/HQ/R.8a/Vol. IX/3799), and University College London, UK (21569/002).

6.4. Results

6.4.1. Characteristics of participants

In total, I enrolled 203 adult household contacts of 111 persons with TB. The majority of these contacts (76.8%, 156/203) were from South Africa, linked to 81 persons with TB (Figure 6-4). In addition, I enrolled 135 adults from 81 neighbourhood households in South Africa. In Tanzania, I enrolled 25 adults from 17 neighbourhood households. I could not enrol additional 13 households to match the number of households with an index person with TB due to refusal. Among the 17 households, one was enrolled in the City of Mbeya. Overall, 16

out of 98 (16.3%) neighbourhood households were enrolled from rural sites in Tanzania through non-random sampling.

Table 6-2 presents the participant characteristics of the combined cohort. The median age was 40.0 years among contacts and 42.0 years among controls, respectively. There were more females among household contacts than in neighbourhood households (66.5% vs. 50.0%). Characteristics by country are presented in Table 6-3.

Figure 6-4. Enrollment of participants

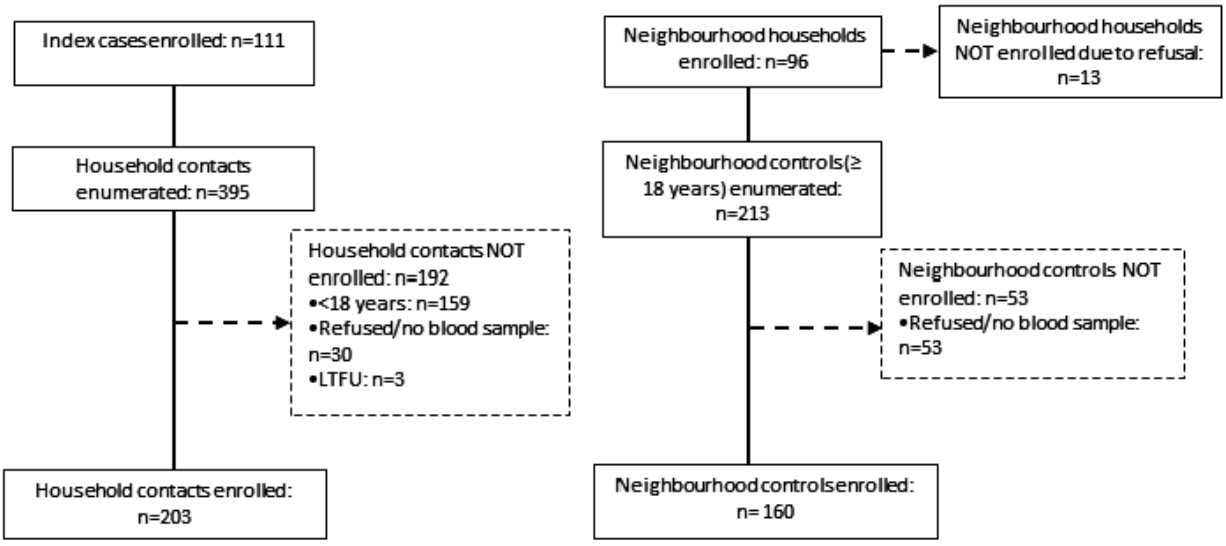


Table 6-2. Characteristics of study participants

	Household contacts (N = 203)	Neighbourhood household members (N = 160)
Country		
South Africa (%)	156 (84.4)	135 (76.8)
Tanzania (%)	47 (15.6)	25 (23.2)
Age (median [IQR])	40.0 [30.0, 59.0]	42.0 [31.0, 56.0]
Female (%)	135/203(66.5)	80/160 (50.0)
Current smoker (%)	33/203 (16.3)	42/160 (26.2)
Alcohol use (%)	78/203 (38.4)	86/160 (53.8)
Obesity (BMI ≥ 30 Kg/m^2) (%)	35/201 (17.4)	18/160 (11.2)
BMI (median [IQR])	24.2 [20.4, 28.1]	21.3 [18.3, 25.7]
Known HIV-positive status (%)	29/203 (14.3)	21/160 (13.1)
Years of education (median [IQR])	10 [7-12]	11 [8-12]
Employment		
Employed (%)	25 (12.3)	12 (7.5)
Self-employed (%)	44 (21.7)	30 (18.8)
Unemployed (%)	119 (58.6)	108 (67.5)
Others (%)	15 (7.4)	10 (6.2)

Note: denominators vary because of missing data

IQR: interquartile range; BMI: body mass index; HIV: human immunodeficiency virus

Table 6-3. Characteristics of participants by country

	South Africa		**Tanzania**	
	Household contacts (N = 156)	Neighbourhood household members (N = 135)	Household contacts (N = 47)	Neighbourhood household members (N = 25)
Age (median [IQR])	42.5 [30.0, 61.3]	40.00 [31.0, 54.5]	37.0 [29.5, 48.5]	49.0 [33.0, 60.0]
Female (%)	101 (64.7)	67 (49.6)	34 (72.3)	13 (52.0)
Current smoker	33 (21.2)	41 (30.4)	0 (0.0)	1 (4.0)
Alcohol use	62 (39.7)	76 (56.3)	16 (34.0)	10 (40.0)
Obesity (BMI ≥ 30 Kg/m^2)	25.1 [20.1, 28.6]	20.6 [17.9, 25.1]	23.1 [21.4, 25.2]	24.8 [22.0, 26.5]
BMI	31 (20.1)	16 (11.9)	4 (8.5)	2 (8.0)
Known HIV-positive status	25 (22.5)	17 (18.3)	4 (11.4)	4 (17.4)

IQR: interquartile range; BMI: body mass index; HIV: human immunodeficiency virus

6.4.2. Prevalence of NCD and multimorbidity

Among household contacts, 23 had diabetes (12.2%, 95% CI 8.3-17.6), of which 17 (73.9%) were newly identified (Table 6-4). Hypertension was present in 39.2% of contacts, and more than half (55.7%, 44/79) were newly identified, and 10.0% (19/190) had CKD. Overall, at least one NCD was present in 49.5% of contacts. The proportion of individuals with > 20% risk for developing CVD was around 3% in both contacts and controls (3.2%, 95% CI 1.4-7.0 vs. 4.0%, 95% CI 1.8-8.5).

When stratified by country, the prevalence of diabetes among contacts was 11.8% in South Africa and 13.3% in Tanzania, and the prevalence of hypertension was 40.8% and 34.0%, respectively (Table 6-5).
When compared with neighbourhood controls, the prevalence of at least one NCD was similar (49.5% 95% CI 42.4-56.5 vs. 51.6% 95% CI 43.5-59.7). When adjusted for age and gender, household contacts did not have a higher likelihood for having at least one NCD than neighbourhood controls (OR 0.85, 95% CI 0.50-1.45). Likewise, the prevalence of individual NCD was similar between contacts and neighbourhood controls overall (Table 6-4) and in South Africa, but perhaps higher among controls in Tanzania (Table 6-5).

Table 6-4. Prevalence of NCD among household contacts and neighbourhood controls

Variable	Household contacts		Controls		Household contacts vs controls
	n/N	% (95% CI)	n/N	% (95% CI)	Adjusted OR* (95% CI), p-value
Diabetes	23/189	12.2 (8.3-17.6)	21/149	14.1 (9.2-21.0)	0.73 (0.37-1.46), p = 0.38
Newly identified diabetes	17/189	9 (5.7-14)	18/152	11.8 (7.4-18.4)	0.65 (0.32-1.35), p = 0.25
Hypertension	79/199	39.7 (33.1-46.7)	71/159	44.7 (36.9-52.7)	0.68 (0.4-1.14), p = 0.14
Newly identified hypertension	44/199	22.1 (16.9-28.4)	37/159	23.3 (17.2-30.6)	0.9 (0.53-1.52), p = 0.68
Chronic kidney disease	19/190	10 (6.5-15.2)	14/157	8.9 (5.3-14.5)	1.65 (0.7-3.9), p = 0.25
Cardiovascular disease risk ≥ 20% over 10 years	6/187	3.2 (1.4-7.0)	6/151	4.0 (1.8-8.5)	0.72 (0.18-2.91), p = 0.65
At least one NCD	93/190	49.5 (42.4-56.5)	79/153	51.6 (43.5-59.7)	0.85 (0.50-1.45), p = 0.56
Multimorbidity**	34/203	16.7 (12.2-22.6)	33/160	20.6 (14.9-27.8)	0.83 (0.46-1.51), p = 0.54
Current smoker	33/203	16.3 (11.7-22.2)	42/160	26.2 (19.8-33.9)	0.84 (0.47-1.52), p = 0.57
Alcohol use	78/203	38.4 (31.9-45.3)	86/160	53.8 (45.8-61.5)	0.6 (0.38-0.95), p = 0.03
Obesity	35/201	17.4 (12.8-23.3)	18/160	11.2 (7.2-17.2)	1.41 (0.73-2.73), p = 0.3

*Adjusted for age and gender

**Two or more conditions of diabetes, hypertension, chronic kidney disease, and HIV.

NCD: non-communicable disease; OR: odds ratio; CI: confidence interval

Table 6-5.Prevalence of NCD among household contacts and neighbourhood controls by country

	South Africa					Tanzania				
	Household contacts		Controls		Household contacts vs controls	Household contacts		Controls		Household contacts vs controls
Variable	n/N	% (95% CI)	n/N	% (95% CI)	OR* (95% CI), p-value	n/N	% (95% CI)	n/N	% (95% CI)	OR* (95% CI), p-value
Diabetes	17/144	11.8 (7.5-18.2)	10/126	7.9 (4.3-14.1)	1.17 (0.46-2.96), p = 0.75	6/45	13.3 (6.3-26)	11/23	47.8 (28-68.3)	0.23 (0.05-1.11), p = 0.07
Newly identified diabetes	12/144	8.3 (4.8-14.1)	7/129	5.4 (2.6-11)	1.12 (0.39-3.2), p = 0.83	5/45	11.1 (4.7-24.2)	11/23	47.8 (28-68.3)	0.23 (0.05-1.11), p = 0.07
Hypertension	63/152	41.4 (33.9-49.5)	55/134	41 (32.9-49.7)	0.76 (0.43-1.34), p = 0.34	16/47	34 (21.7-49)	16/25	64 (43.1-80.7)	0.34 (0.09-1.39), p = 0.13
Newly identified hypertension	31/152	20.4 (14.7-27.6)	26/134	19.4 (13.5-27)	0.99 (0.54-1.79), p = 0.96	13/47	27.7 (16.6-42.4)	11/25	44 (26.1-63.6)	0.91 (0.25-3.28), p = 0.89
Chronic kidney disease	18/144	12.5 (8-19)	14/132	10.6 (6.4-17.1)	1.33 (0.55-3.25), p = 0.53	1/46	2.2 (0.3-13.9)	0/25	0 (0-0)	-
Cardiovascular disease risk ≥ 20% over 10 years	5/142	3.5 (1.5-8.2)	6/128	4.7 (2.1-10)	0.4 (0.08-1.97), p = 0.26	1/45	2.2 (0.3-14.2)	0/23	0 (0-0)	-
At least one NCD	75/144	52.1 (43.9-60.2)	60/128	46.9 (38.2-55.7)	1.03 (0.57-1.85), p = 0.93	19/46	41.3 (28.5-55.4)	19/25	76 (55.3-89)	0.27 (0.07-1.04), p = 0.06
Multimorbidity**	28/156	17.9 (12.7-24.8)	22/135	16.3 (11-23.6)	1.02 (0.51-2.03), p = 0.96	6/47	12.8 (5.8-25.8)	11/25	44 (25.1-64.8)	0.42 (0.09-1.89), p = 0.26
Current smoker	33/156	21.2 (15.3-28.4)	41/135	30.4 (23-38.9)	0.85 (0.46-1.57), p = 0.6	0/47	0 (0-0)	1/25	4 (0.6-23.7)	0 (0-0), p = 0.00
Alcohol use	62/156	39.7 (32.3-47.7)	76/135	56.3 (47.6-64.6)	0.61 (0.36-1.02), p = 0.06	16/47	34 (22-48.5)	10/25	40 (23.2-59.5)	1.04 (0.25-4.36), p = 0.96
Obesity	31/154	20.1 (14.5-27.2)	16/135	11.9 (7.4-18.5)	1.45 (0.72-2.91), p = 0.3	4/47	8.5 (3.2-20.7)	4/47	8 (2-27.1)	2.95 (0.3-28.76), p = 0.35

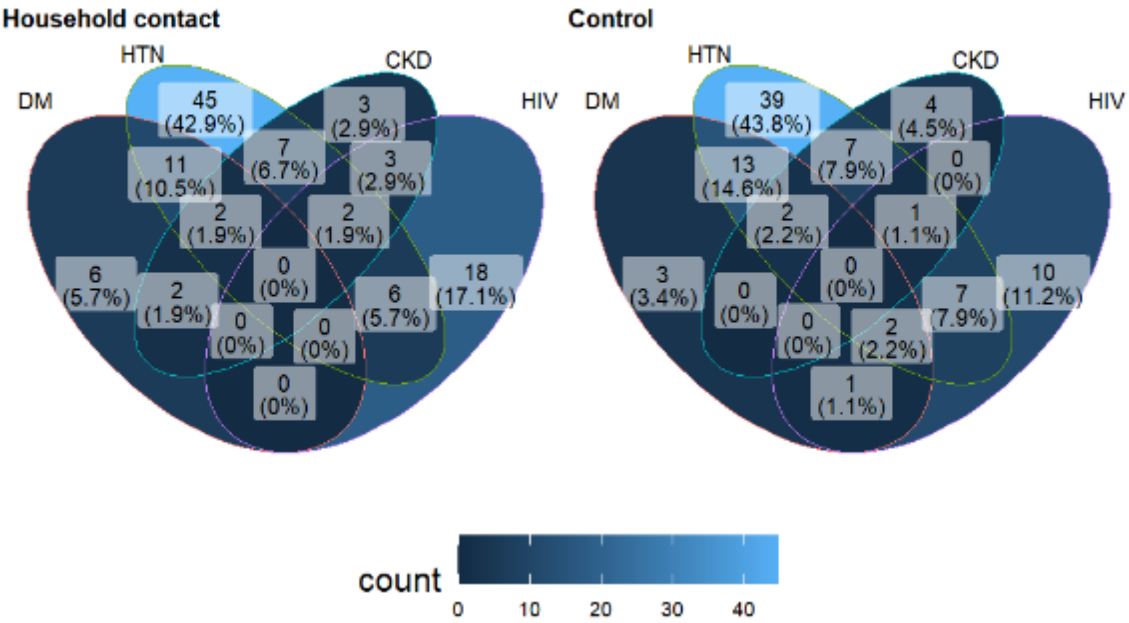
*Adjusted for age and gender.

**Two or more conditions of diabetes, hypertension, chronic kidney disease, and HIV.

NCD: non-communicable disease; OR: odds ratio; CI: confidence interval

Among household contacts, 16.7% (95%CI 12.2-22.6) had multimorbidity comprising at least two conditions out of NCD and HIV, compared to 20.6% (95% CI 14.9-27.8) among controls. Figure 6-5 presents the pattern of NCD overlap and multimorbidity. Diabetes and hypertension were most commonly overlapping; among 34 contacts with multimorbidity, 13 (38.2%) had both diabetes and hypertension. A similar pattern was observed in neighbourhood controls.

Figure 6-5.The pattern of multimorbidity among household contacts and controls



DM: diabetes mellitus; HTN: hypertension; CKD: chronic kidney disease; HIV: human immunodeficiency virus

6.5. Discussion

The pilot study found a high prevalence of NCD, including diabetes and hypertension, most of which were undiagnosed prior to the present study. For instance, the prevalence of diabetes was 12.2% among contacts, and around 70% of them were newly diagnosed. The large proportion of contacts with undiagnosed NCD suggests that integrating screening for NCD within contact investigations would help identify those who are otherwise unaware of their NCD. Furthermore, people with diabetes are at an increased risk for TB, especially if their glycaemic levels are poorly controlled.[174,250] Thus, early identification and treatment of contacts with diabetes might help reduce TB incidence. A recent cluster RCT demonstrated the

effect of nutritional supplementation in preventing TB among household contacts.[137] However, the impact of an integrated care approach addressing TB, diabetes, and other NCDs has not been evaluated. To evaluate the effectiveness of this integrated program, a similar RCT is needed. Importantly, the outcomes of this trial should extend beyond TB incidence, capturing the broader health implications, including NCD outcomes. This will provide a more complete picture of an integrated healthcare strategy. Additionally, the feasibility and acceptability of this integrated approach among household members, healthcare workers, and national programs outside the study setting need to be evaluated.

Contrary to previous studies,[141,209,221,224] my study included a control group from randomly selected neighbourhood households and accounted for demographic differences. I found a similarly high prevalence of NCD both in household contacts and neighbourhood controls. Therefore, screening for NCD might warrant extension to people in the same community. Depending on the feasibility, multiple options could be considered. For example, contact investigations could involve neighbourhood households for both TB and NCD screening. Alternatively, WHO recommends systematic screening for TB disease among the general population in areas with a high TB prevalence.[112] NCD screening could be integrated into such community-wide TB screening activities. Of note, due to the low statistical power in my study, I cannot rule out a difference in the NCD prevalence between contacts and neighbourhood controls.

No study to date has evaluated multimorbidity among contacts of TB. Consistent with my prior knowledge, diabetes and hypertension, both of which are known to increase CVD risk, overlapped most commonly.[251] In my cohort, 3.2% of contacts had a≥ 20% risk of developing CVD within ten years, warring statin therapy.[124] The risk may be heightened by HIV co-infection[252] and by TB.[39] WHO recommends assessment of CVD risk in individuals at risk for CVD, such as people aged > 40 years and smokers. It is a missed opportunity not to conduct CVD risk assessment in contacts who have these conditions to prevent CVD.

There are limitations in my study. First, I could not enrol the target number of index and control households due to the delay in initiating this pilot study and a faster recruitment into the parent study. Furthermore, the number of participants per

household was smaller than expected, especially among neighbourhood control, because of unavailability at the time of the household visit and lack of motivation for NCD screening. It may be possible that people who were at risk for NCD were overrepresented. In addition, integrated TB and NCD screening may also face low participation rates, and strategies to promote participation are needed to maximise the cost-effectiveness and impact of the screening. Second, in rural Tanzanian sites, operational challenges prevented the random selection of control households. The median age was higher (49 years) than contacts (37 years), and around 50% had diabetes. This may have increased the participation of older people and those with co-morbidity, probably influenced by availability and willingness to participate in the study. Nonetheless, the results are similar when restricted to South Africa. Third, the ascertainment of NCD, including hypertension, was based on a measurement on a single day. Therefore, the NCD prevalence might have been overestimated.[253]

6.6. Conclusion

In summary, the pilot study highlights a high prevalence of undiagnosed NCDs, particularly diabetes, among contacts of persons with TB and individuals in the same communities. However, the study's sample size, intended as a pilot, precluded demonstrating a difference in the NCD prevalence between household contacts of persons with TB and individuals in the same neighbourhoods. A larger study is warranted to determine whether NCD screening in contacts leads to higher yields than non-targeted screening of people in the community, such as door-to-door screening and screening camps. Nonetheless, the high prevalence of undiagnosed NCDs underscores the potential benefits of NCD screening as an extension of existing TB contact investigations. Future studies should evaluate the comprehensive health benefits of such integrated care among contacts. Furthermore, comparable NCD prevalence observed in individuals from the same neighbourhoods as TB contacts suggests a potential rationale for expanding NCD screening to encompass the wider community. Further studies are needed to evaluate the effectiveness, feasibility, and acceptability of these expanded, integrated TB and NCD screening programmes.

7. Costs and cost-effectiveness of integrated NCD screening within TB contact investigations

7.1. Abstract

Background

The integration of NCD screening within household TB contact investigations may help identify individuals with undiagnosed NCD and reduce the burden of both TB and NCD. However, data on the costs and cost-effectiveness of this integrated screening approach are lacking.

Method

I conducted a cross-sectional study in South Africa to collect patient and provider costs associated with NCD screening (i.e. hypertension, diabetes, chronic kidney disease, and dyslipidaemia). I estimated the incremental costs for screening per NCD case identified. Additionally, I used a decision tree model to estimate the incremental costs of NCD screening and treatment per disability-adjusted life year (DALY) averted over a 10-year time horizon from a healthcare perspective. CVD risk over 10 years was estimated using the WHO prediction model.

Results

The total incremental cost for NCD screening was US$ 72.3 per contact screened. The incremental cost per identified NCD case was US$ 334.0, with provider costs accounting for the majority (US$ 331.5, 99.3%). Integrated NCD screening was associated with a mean decline in 10-year CVD risk, from 5.7% to 2.7% among contacts found to have NCDs through screening. The study found an incremental cost-effectiveness ratio of US$ 24,940.0 per DALY averted, which exceeded the cost-effectiveness threshold of US$ 3,708 per DALY averted in South Africa. Management of NCDs identified through screening accounted for over 80% of the total incremental costs.

Conclusion

This study did not establish the cost-effectiveness of integrated NCD screening within household contact investigations. The breakdown of the costs suggested that the cost-effectiveness of the integrated screening largely depends on the cost-

effectiveness of subsequent care, mainly drug costs. The high ICER may also have been influenced by limitations in the study's methodology, such as the restriction to CVD outcomes. Future cost-effectiveness studies should incorporate empirical data on the impact of integration on both TB and NCD outcomes evaluated through trials.

7.2. Introduction

TB poses a significant economic burden to patients and their households. To address this, one of the three targets of the End TB strategy aims to eliminate catastrophic costs for TB-affected households by 2030.[114] National TB cost surveys in 27 LMIC reported between 13% and 92% of TB-affected households experience substantial costs exceeding > 20% of annual household income.[1] Direct medical costs accounted for up to 20-40% of total costs despite the presence of "TB free care" policies in some countries like Mali, Kenya, Ghana and Mongolia.[1] The situation may be further exacerbated by the dual burden of TB and NCD within the same households.[254,255]

While expanding prevention and control measures for NCD may initially increase health system costs, the WHO estimates a substantial return on investment in public health interventions for NCD. They are projected to save around 7 million lives and avoid 10 million cases of heart disease and stroke, adding a total of 50 million years of healthy life.[256] This reduction in deaths and morbidity would result in economic and social benefits worth more than US$ 230 billion, yielding a return of US$ 7 for every dollar spent on NCD interventions. In particular, WHO recommends a list of "best buy" interventions for NCD, which are considered cost-effective and feasible because of an incremental cost-effectiveness ratio of ≤ I$100/DALY using the WHO's CHOICE model. [257] One such intervention is the management of CVD risk in persons with a high risk (10-year CVD risk ≥30% or ≥20% depending on the resource availability), which involves treatment of hypertension, diabetes, and statin therapy.[257]

Despite these insights, there remains a significant gap in the literature regarding the economic implications of integrating NCD screening within TB contact investigations. Such integration offers a promising avenue to enhance NCD control and improve cost-effectiveness by leveraging existing resources and infrastructure. However, evidence on the costs and cost-effectiveness of this approach is sparse. Only a single study conducted in Myanmar estimated the cost-effectiveness of diabetes screening within TB contact tracing. [258] The study found an incremental cost of US$ 213.87 per DALYs averted. The authors used a GDP-based willingness to pay threshold of US$ 1250 (one GDP per capita) and reported that diabetes screening

was cost-effective. However, the study did not evaluate the screening of other NCD and only considered the costs at the initial two visits.

To fill this knowledge gap, I estimated the costs and cost-effectiveness of integrated NCD screening within household contact investigations in South Africa.

7.3. Method

7.3.1. Design

I collected costs for screening NCD (hypertension, diabetes, CKD, and dyslipidaemia) integrated within household contact investigations as part of the pilot clinical study in Ekurhuleni, South Africa reported in Chapter 6. (see Chapter 6 for details). I estimated incremental screening costs per NCD detected for providers and patients, respectively. The included costs were limited to those incurred up to the point of referral (e.g. travel and consultation; see 7.3.3 for details) and did not include treatment costs for NCDs.

Additionally, I performed a decision tree analysis to estimate the incremental costs per DALY averted over a 10-year period from the perspective of the healthcare system, using an approach similar to that of Sando et al.[259] For estimating the incremental costs per DALY averted, I did not include a societal perspective due to the limited availability of data on societal costs related to long-term NCD care and treatment.

7.3.2. Intervention description

In the integrated screening, household contacts of people with TB underwent health questionnaires and screening for hypertension, diabetes, CKD, and dyslipidemia. A study nurse measured blood pressure and conducted blood tests for diabetes (random blood glucose and HbA1c), serum creatinine, and total cholesterol. The blood samples were sent to our laboratory on the same day. Contacts newly diagnosed with NCDs were referred to a nearby clinic for further management.

I assumed that referred contacts received treatment in accordance with the South African PC 101 guideline, following a recent cost-effectiveness analysis by Basu et al. [260,261] For simplicity, based on initial blood pressure and HbA1c levels, I assumed that contacts would start a full set of treatment likely necessary to achieve the

treatment targets (SBP < 140 and HbA1c < 7.0%), rather than titrating over time. For isolated diastolic hypertension, I assumed that contacts would only receive the first-line drug. Table 7-1 summarizes the detailed assumption of treatment.

Table 7-1. Treatment algorithm

Hypertension	
SBP 140-149 OR (SBP < 140& DBP ≥ 90)	Diuretics
SBP 150-159	Diuretics+ACEI
SBP160-169	Diuretics+ACEI+Ca-blocker
≥ SBP170	Diuretics+ACEI+Ca-blocker+beta-blocker
Diabetes	
HbA1c 6.5- 8.5	Metformin
HbA1c 8.5-10	Metformin + Sulfonylurea Glibenclamide
HbA1c >10	Metformin + Sulfonylurea Glibenclamide+ insulin, basal
Statin	
History of cardiovascular disease OR 10-year cardiovascular disease risk >20% OR diabetic with hypertension, obesity, smoking, or older than 40 years of age	Statin

SBP: systolic blood pressure; DBP: diastolic blood pressure; ACEI: Angiotensin-converting enzyme inhibitor

The baseline risk for developing CVD was estimated over 10 years using the WHO risk prediction model employing the "whocvdrisk" command in STATA (see Figure 6-2 and 6-3 for parameters).[124] For the effectiveness of interventions to reduce CVD risk, I used parameters from Basu et al. and Kasaie et al (Table 7-2).[260,262] The relative risk reduction of CVD due to hypertension treatment was estimated using the Smith-Spangler equation, which calculates relative risk based on age and change in systolic blood pressure (Table 7-2).[263,264] The expected reduction in systolic blood pressure from each drug was based on estimates from a meta-analysis. [265] For diabetes treatment, I assumed a RR of CVD of 0.79 (95% CI 0.64-0.98) compared to no treatment, like Kasaie et al.,[262] based on a meta-analysis of the effects of metformin. [266] When multiple interventions are given, the overall reduction in risk was assumed to be multiplicative. I did not account for a potential reduction in CVD risk through changes in HbA1c levels because the cardiovascular benefits of other diabetes therapies are less definitive[267,268], and the WHO model for predicting CVD risk does not incorporate baseline HbA1c levels.

Table 7-2.Effectiveness of interventions

SBP reduction	Reduction in systolic blood pressure (mmHg, 95% CI)	Source
ACE inhibitor	8.5 (7.9, 9.0)	Law, et al.[265] cited by Basu et al.[260]
Beta-blocker	9.2 (8.6, 9.9)	
Thiazide diuretic	8.8 (8.3, 9.4)	
Calcium channel blocker	8.8 (8.3, 9.2)	
Relative risk reduction		
Relative risk for atherosclerotic cardiovascular disease events according to s a function of age (in years) and change in systolic blood pressure (ΔSBP)	$RR = 2^{\Delta SBP(-0.0000184775\times age2+0.001584\times age+0.028672)}$	Smith-Spangler, et al.[263] cited by Basu et al.[260]
Risk for CVD in people treated for diabetes	RR= 0.79 (95% CI 0.64-0.98)	Lamanna, et al.[266] cited by Kasaie, et al.[262]
Relative risk for CVD in people given statin therapy	RR= 0.79 (95% CI 0.77-0.81)	Cholesterol Treatment Trialists' Collaboration, 2015.[269] cited by Basu et al.[260]

ACE: Angiotensin-converting enzyme; SBP: systolic blood pressure; RR: relative risk; CVD: cardiovascular disease; ACE: Angiotensin-converting enzyme inhibitor

7.3.3. Estimating costs

As part of my cross-sectional study (see Chapter 6), I estimated the costs required for NCD screening and care integrated within household contact investigations. First, I interviewed research staff conducting household investigations to understand the extra time spent on NCD screening in addition to TB investigations. I then combined this time with their hourly wages, which were obtained from the project's financial records, to estimate human resource costs. Additionally, costs for laboratory tests, equipment (e.g., blood pressure monitors), and training were abstracted from the financial records. Second, I administered a questionnaire to study participants who were found to have NCD to estimate both direct and indirect costs. The questionnaire was developed by adapting previous tools used by WHO TB patient cost surveys.[270] The information collected included time spent for travel and in clinics, costs for transportation, meals, and clinic attendance, as well as income losses of participants themselves and their attendants (if any). Costs were converted from ZAR to US$ using the 2022 World Bank exchange rate.

In addition to the costs for integrated screening at the baseline, I estimated the costs for the subsequent management of NCD at healthcare facilities, adopting the estimates by Basu et al. (Table 7-3).[260] Briefly, Basu et al. estimated costs for the treatment of each NCD by breaking them down into care components as per the standard guidelines. They then extracted costs for these from national data sources, including the South African Uniform Patient Fee schedule and the National Health Laboratory Service fees. For contacts with multiple concurrent risk factors or conditions, the cost of annual physician visits, nurse visits, other services, and overlapping laboratory tests or medications were counted only once.

Costs were discounted at 3% per year. In the scenario without integrated screening, I assumed that contacts would start treatment for their underlying NCD once they develop CVD at year 5. For contacts who do not develop CVD, I assumed that no treatment is given.

Table 7-3.Costs for the management of NCD

Condition	Item	Cost (US$)
Hypertension	Annual physician visit*	20/yr
	Nurse visit every three months	37/yr
	Annual electrolytes and urea labs	9/yr
	Thiazide	52/yr
	ACE inhibitor	69/yr
	Calcium channel blocker	34/yr
	Beta-blocker	36/yr
Dyslipidaemia	Annual physician visit	20/yr
	Statin	34/yr
Type 2 diabetes mellitus	Annual physician visit	20/yr
	Nurse visits every three months	37/yr
	Hemoglobin A1c every 6 months	13/yr
	Annual electrolytes and urea labs	9/yr
	Metformin	62/yr
	Sulfonylurea	204/yr
	Insulin, basal	115/yr
Ischemic heart disease	Acute care for IHD	1089 (once)
	Monthly nurse visits for 6 months	55
	annual physician follow-up	20/yr

	Asprin	1/yr
	Beta-blocker	36/yr
	Statin	34/yr
	ACE inhibitor	125/yr
	IHD – electrolytes and urea every 6 months	17/yr
Stroke	Acute care for stroke	2202 (once)
	Monthly nurse visits for 6 months post-stroke	55/yr
	Stroke – aspirin 1/yr	1/yr
	Stroke – statin	34/yr
	Annual physician follow-up	20/yr

IHD: ischemic heart disease; ACE: Angiotensin-converting enzyme

7.3.4. Outcome

I adapted the approach used by Sando et al.[259] For contacts who were newly found to have NCD, I estimated individual risk for CVD over a 10-year period using the WHO risk prediction model.[124] Based on the 2019 GBD estimate of South Africa, I assumed 60% of CVD events were ischemic heart disease and 40% stroke.[4] I did not consider other outcomes (e.g. diabetic retinopathy and renal failure) due to a lack of variables in my dataset to reliably estimate their risk. For each CVD event, I calculated Years of Life Lost (YLL) and Years Lived with Disability (YLD), using case fatality ratios based on the 2019 GBD study.[4] I assumed that CVD events would occur at a mid-time point (i.e., year 5) and then estimated YLLs and YLDs using age-sex-specific life expectancies for a maximum of 5 years following the event.[271] For disutility weights, I adopted one for atherosclerotic cardiovascular disease that was used by Basu et al.[260] Table 7-4 presents parameters used to calculate DALYs. I calculated DALYs for each scenario (integrated NCD screening vs no screening) by summing up YLLs and YLDs, and DALYs were discounted at 3% per year.

Table 7-4.Parameters used to calculate DALYs.

		Source
Risk for CVD	Prediction model over 10 years (60% of CVD events are assumed to be IHD, based on GBD 2019)	WHO risk prediction model
Case fatality due to IHD	28.6%	GBD 2019 (approximated by deaths/incidence)
Case fatality due to Stroke	42.1%	GBD 2019 (approximated by deaths/incidence)
Disutility due to CVD	0.28 (0.06, 0.57)	Basu, 2018

IHD: ischemic heart disease.

7.3.5. Analysis

Incremental costs per NCD identified

First, I calculated incremental provider, patient, and total costs, respectively. Since I did not collect the costs for baseline contact tracing activity costs, I directly estimated the incremental costs based on the data outlined in the preceding sections. The costs included those required for conducting screening in households and subsequent clinic visits for the initial investigation of contacts found to have NCD but did not include downstream costs associated with treatment. Indirect costs (i.e. loss of income by contacts and their attendants) were estimated in two ways. First, I used self-reported income loss. However, as discussed by Pillai et al.,[272] the use of self-reported income underestimates the productivity loss of non-waged workers. Thus, following Pillai et al.,[272] I used an alternative approach of 'the minimum wage approach', using the minimum hourly wage in 2022 (US$1.42) multiplied by the time spent at the clinic and travelling.

Second, I calculated the number of newly identified NCD cases in both the intervention and baseline scenarios. In the baseline scenario, no cases were assumed to be identified, so the incremental number of cases identified was considered equal to the absolute number identified in the intervention scenario.

Finally, I calculated the incremental costs per new NCD case identified.

Incremental costs and DALYs averted over 10 years

I examined the potential costs and DALYs averted associated with the integration of screening and subsequent treatment for NCD in contact who are newly found to have

NCD, compared to no treatment, using a simple decision tree (Figure 7-1). I modelled outcomes (incremental costs and DALYs averted) 10 years into the future from a health care perspective. The incremental cost-effectiveness ratio was estimated as incremental costs per DALY averted (ICER).

WHO recommends the assessment of CVD risk and testing for diabetes in individuals with high risk (Table 7-5). In view of this, I tested three different strategies where screening of NCD is limited to certain groups:

Strategy 1: All adults > 40 year

Strategy 2:

- CVD risk assessment and blood pressure measurement:
  - Adults aged > 40 years;
  - Current smokers; or
  - People who are overweight
- Testing for diabetes
  - Adults aged > 40 years who are overweight

Strategy 3:

- CVD risk assessment and blood pressure measurement:
  - Adults aged > 40 years;
  - Current smokers; or
  - People who are overweight
- Testing for diabetes
  - Adults aged > 40 years who are obese

Sensitivity analysis

To evaluate the impact of the uncertainty of parameters and NCD prevalence in my study, I performed a probabilistic sensitivity analysis. I first assigned appropriate distributions to parameters—beta for disutility, normal for systolic blood pressure reduction, and log-normal for RR—to mirror their statistical properties. A random sample from each distribution was drawn. Subsequently, the study cohort was resampled with replacement to simulate the variability inherent in the sample population. Lastly, I repeated the calculation of incremental costs per DALY averted 10,000 times with these parameters. I presented the distributions of the incremental costs per DALY averted. I also calculated the net health benefit and presented the

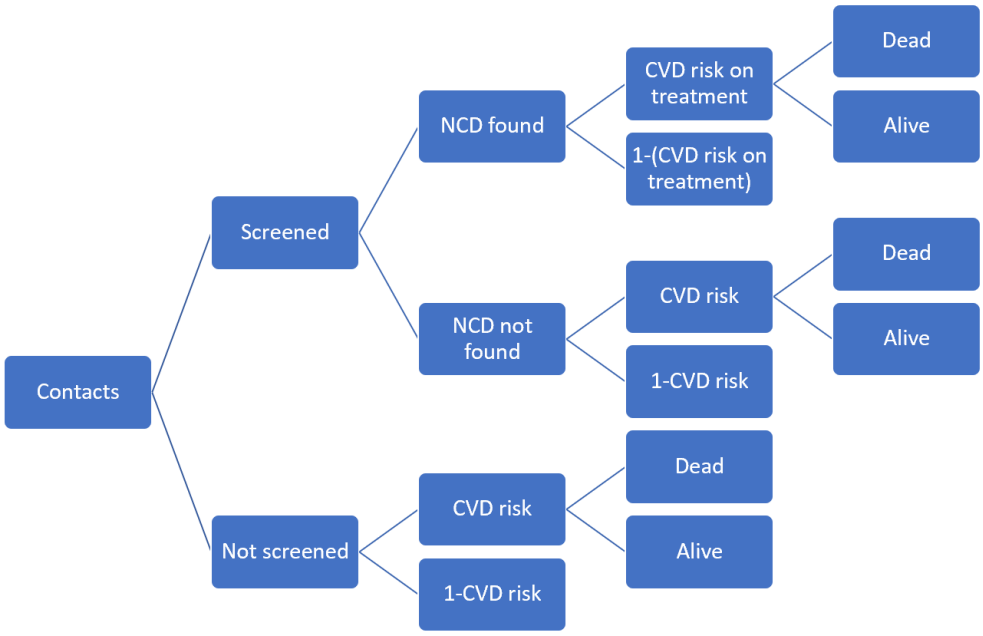
2.5th and 97.5th percentiles as uncertainty intervals. The net health benefit was estimated as follows[273]:

incremental DALYs averted - (incremental cost/opportunity cost threshold)

For the opportunity cost threshold, I used the cost-effectiveness threshold in South Africa proposed by Edoka et al., which was US$3015 per DALY in 2015.[274] This amount was inflated using an annual inflation rate of 3% for 2022, resulting in US$3708. I did not use GDP-based thresholds, such as 1 to 3 times the GDP per capita. WHO no longer recommends these thresholds because they do not reflect the opportunity cost of health spending.[275]

Additionally, I conducted a scenario analysis to evaluate changes in cost-effectiveness by increasing the 10-year risk for CVD. I increased the CVD risk from 1.1 to 5.0-fold in increments of 0.1, while accounting for uncertainty in the parameters. The probability of the intervention being cost-effective, defined as an ICER below US$3708, was calculated. I plotted the median CVD risk in the study population against the probability of being cost-effective.

Figure 7-1.Decision tree



CVD: cardiovascular disease; NCD: non-communicable disease

Table 7-5. WHO recommendations on CVD assessment and testing for diabetes

CVD risk assessment	Diabetes
Aged > 40 years Smokers Overweight Known hypertension Known diabetes History of premature CVD in first degree relatives History of diabetes or kidney disease in first-degree relatives	Adults who are symptomatic, or aged > 40 years and who are overweight (BMI > 25), or obese (BMI > 30), or follow national guidelines

CVD: cardiovascular disease; BMI: body mass index

7.4. Results

I enrolled 291 participants, of whom 63 with NCD were referred to the clinic. Among those, 54 visited the clinic, and 44 participated in a survey to collect screening costs. The mean age was 56.5 years, and about half (56.8%) were female.

Table 7-6. Characteristics of participants who participated in the cost survey

Variables	Participants (N = 44)
Age (median [IQR])	56.50 [42.00, 67.00]
Female (%)	25 (56.8)
Current smoker (%)	8 (18.2)
Alcohol use (%)	14 (31.8)
Obesity (BMI ≥ 30 Kg/m^2) (%)	8 (18.2)
BMI (median [IQR])	22.88 [20.07, 27.39]
Known HIV-positive status (%)	1 (4.2)
Hypertension	42 (95.5)
Diabetes	9 (22.0)
Source of income	
Depending on others (%)	11 (25.0)
Grant/pension (%)	17 (38.6)
Salary/wage/business (%)	6 (13.6)
Others (%)	10 (22.7)

7.4.1. Costs for integrated NCD screening

Table 7-7 summarises the results of the cost survey. All but one participant visited a public clinic. None of those who visited a public clinic paid registration fees.

Furthermore, no participants needed to pay for tests or medications. Only two participants reported an income loss of US$12.2 and 33.6, respectively.

Table 7-7. Results of patient cost survey

Variables	Median (IQR) or N (%) unless otherwise indicated
Type of facilities visited	
Public clinic (%)	43 (97.7)
General practitioner (%)	1 (2.3)
Number of clinic visits	
Once	42 (95.5)
Twice	2 (4.5)
Travel time, min (IQR)	30.0 (20.0, 40.0)
Clinic time, min (IQR)	90.0 (43.75, 150.0)
Costs for meal, $ (IQR)	0 (0, 0), five needed to pay for meal, from $0.61 to 1.22
Costs for registration	Only one needed to pay USD 27.5
Costs for examinations or medicine	None required.
Self-reported income loss	Only two reported loss of income-$12.2 and 33.6
Need for an attendant (%)	
Yes	11 (25%)
No	33 (75%)
Need to buy equipment	One bought a blood pressure monitor ($ 18.3)

The self-reported income loss per referred individual amounted to US$ 0.76 on average, in contrast to US$3.18 calculated using the minimum wage approach. When combining both direct and indirect costs, the total costs based on self-reported income reached US$ 2.93. This figure rose to US$ 5.14 when using the minimum wage approach.

Table 7-8. Patient costs for NCD screening

	Average cost per person who was referred (USD)
Direct costs	
Equipment	0.42
Transportation cost	1.59
Meal	0.09
Registration	0.49
Total direct costs	2.59
Indirect costs	
Self-reported income loss	0.76
Income loss for contacts (minimum wage approach)	3.18
Income loss for attendants (minimum wage approach)	0.79
Total indirect costs using self-reported income loss	0.76
Total indirect costs using minimum wage approach	3.97
Total costs	
Total costs using self-reported income	2.93
Total costs using minimum wage approach	5.14

Table 7-9 presents incremental provider costs for NCD screening. Two research assistants and a nurse spent an extra 19 minutes on average to implement NCD screening. This results in incremental personnel costs of US$9.79 per contact screened. The total direct costs for laboratory tests and consumables were US$60.34, with the HbA1c tests contributing the largest share at 38.9%. The total provider cost per contact screened was US$71.6.

Table 7-9. Incremental provider costs for NCD screening

Personnel	**Hourly wage ($)**	**Input**	**Average incremental cost per contact ($)**
Research assistants	8.5	Extra 19 minutes per contact, two assistants	5.38
Nurse	13.9	Extra 19 minutes per contact, one nurse	4.41
Subtotal			9.79
Laboratory tests and consumables	**Unit cost ($)**	**Unit**	**Average incremental cost per contact ($)**
Blood glucose	6.85	One per contact	6.85
HbA1c	23.47	One per contact	23.47
Creatinine Serum	6.85	One per contact	6.85
Total cholesterol	7.82	One per contact	7.82
Sodium Fluoride Glucose Tube	0.27	One per contact	0.27
HbA1c sample collection tube	0.27	One per contact	0.27
Creatinine and T-cho Serum collection tube	0.27	One per contact	0.27
Urine protein dip-stick	0.29	One per contact	0.29
Glove	0.22	One per contact	0.22
Vacutainer needles	0.39	One per contact	0.39
Vacutainer tube holder	0.22	One per contact	0.22
Elastoplast	0.005	One per contact	0.005
Alcohol swabs	0.05	One per contact	0.05
Tourniquet	48.9	One per total number of contacts screened (N = 291)	0.17
Cooler box	48.9	One per total number of contacts screened (N = 291)	0.17
Sharp bins five litres	4.89	One per total number of contacts screened (N = 291)	0.02
Kit construction	1392.67	One per total number of contacts screened (N = 291)	4.79
Transportation cost	1298.78	One per total number of contacts screened (N = 291)	4.46
Blood pressure monitor	45.84	One per total number of contacts screened (N = 291)	0.16
Out-patient consultation	14.55	One per contact referred	3.59
Sub-total			60.34
Programme cost	**Unit cost ($)**	**Unit**	**Average incremental cost per contact ($)**
Training	427.87	One per total number of contacts screened (N = 291)	1.47
Sub-total			1.47
Total provider cost per contact screened			**71.6**

Overall, the total incremental cost for NCD screening was US$ 72.3 per contact screened (Table 7-10). The incremental cost per at least one NCD identified was US$ 334.0, most of which was accounted for by provider costs (US$ 331.5, 99.3%).

Table 7-10.Summary of incremental costs for NCD screening

	Incremental cost per person screened (US$)	Incremental cost per NCD identified
Provider cost per person screened	71.6	331.5
Patient cost per person screened	0.72	2.5
Total cost per person screened	72.3	334.0

7.4.2. Cost-effectiveness of integrated NCD screening over 10 years

I modelled the cost-effectiveness of integrated NCD screening in 291 study participants. With the intervention, the median 10-year CVD risk declined from 5.7% (IQR 1.8-12.3) to 2.7% (IQR 1.0-5.1%) (Table 7-11). Consequently, DALYs were reduced from 3.7 years per 100 persons to 1.8 years. The incremental cost for NCD screening was, on average, US$484.9 per contact screened, with 85% of this amount (US$413.2) attributed to the costs of management following the screening. Of the incremental costs for subsequent management, drug costs constituted the majority, accounting for 65%. The ICER was US$24,940.0 per DALY averted. When excluding costs of screening, the ICER was US$21257.3.

Table 7-11.Incremental cost, DALYs averted and cost-effectiveness of integrated NCD screening within contact investigation

\	**Intervention (integrated NCD screening)**	**Status quo**
10-year CVD risk in contacts found to have NCD (%)	Median: 2.7 (IQR 1.0-5.1)	Median: 5.7 (IQR 1.8-12.3)
YLL per 100 persons	1.4	3.0
YLD per 100 persons	0.8	1.6
DALYs (discounted) per 100 persons	1.8	3.7
Incremental cost for screening (US$) per contact screened	71.6	-
Cost for subsequent management (US$) per contact screened	446.7	33.4
Incremental cost per contact screened	484.9	-
Incremental cost per DALY averted (US$)	24940.0	-

Among the primary analysis and three strategies targeting different sub-groups, the ICER was lowest when the screening was restricted to persons over 40 years old, at US$18,911.4 per DALY averted (Table 7-12). When NCD screening was restricted to

groups recommended by the WHO PEN guidelines, the ICER did not substantially differ from the primary analysis.

Table 7-12. Cost-effectiveness of integrated NCD screening within contact investigation- comparison of different targeting strategies

	Primary analysis (All contacts)	**Strategy 1 (> Aged 40 years)**	**Strategy 2 (WHO PEN guidelines[1])**	**Strategy 3 (WHO PEN guidelines[2])**
10-year CVD risk (%)	Median: 2.7 (IQR 1.0-5.1)	Median: 5.7 (1.8-12.3)	Median: 2.7 (IQR 1.2-5.2)	Median: 2.7 (IQR 1.2-6.3)
YLL per 100 persons	1.4	1.5	1.5	1.6
YLD per 100 persons	0.8	0.8	0.8	0.9
DALYs (discounted) per 100 persons	1.8	1.9	1.8	2
Incremental cost for screening (USD) per contact screened	71.6	35.9	38.3	34.5
Cost for subsequent management (USD) per contact screened	446.7	338.2	399.7	361.8
Incremental cost per contact screened	458.2	314	380.5	341.5
Incremental cost per DALY averted (USD)	24940.0	18911.4	20201.87	22149.43

[1]CVD risk assessment and blood pressure measurement in adults aged > 40 years, current smokers, or people who are overweight and testing for diabetes in adults aged > 40 years who are overweight.
[2]CVD risk assessment and blood pressure measurement in adults aged > 40 years, current smokers, or people who are overweight and testing for diabetes in adults aged > 40 years who are obese.

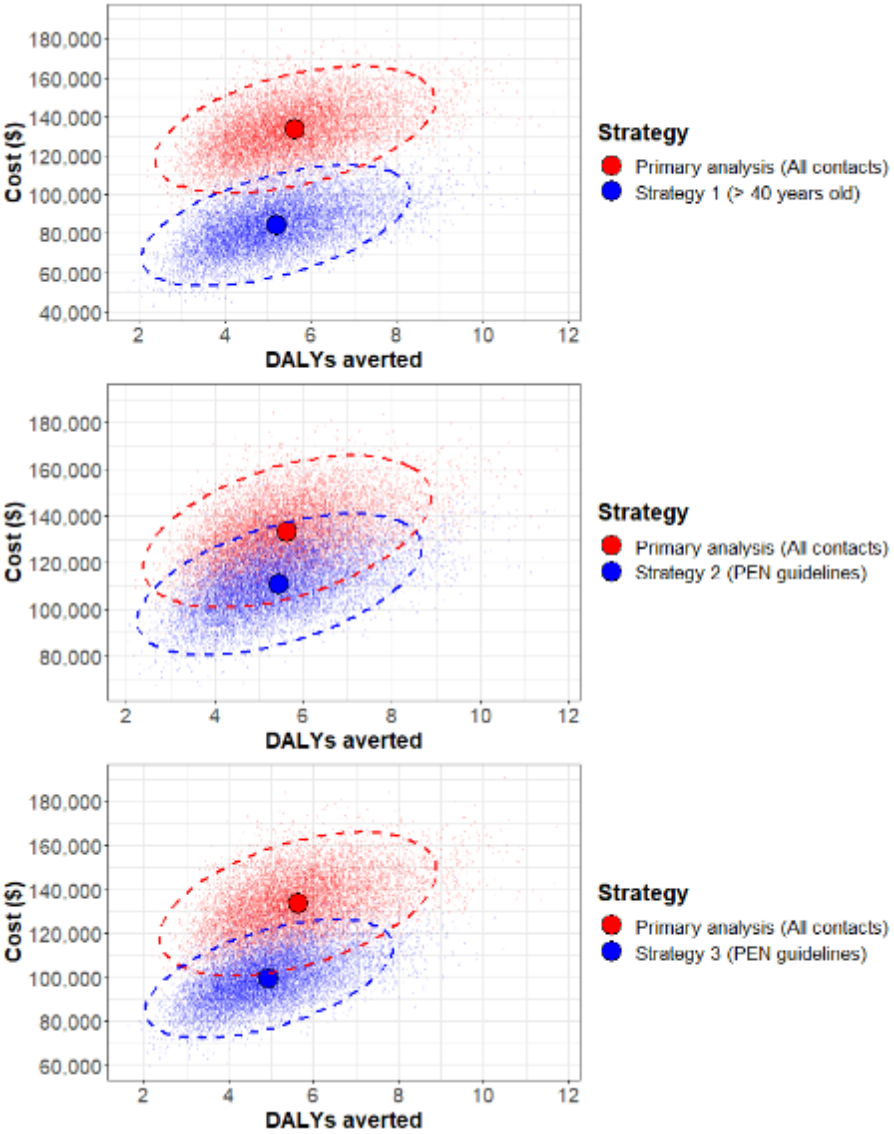
Table 7-13 and Figure 7-2 present the results of the sensitivity analysis. These results indicate that the net health benefits remained negative across all scenarios, suggesting a net loss in health benefits. The upper limit of the uncertainty intervals (i.e., 97.5th percentiles) was largest at -19.9 when NCD screening was restricted to individuals over 40 years old.

Table 7-13. Probabilistic sensitivity analysis of the cost-effectiveness of integrated NCD screening.

	Uncertainty interval of net health benefit
Primary analysis (All contacts)	-50.4; -33.4
Strategy 1 (> Aged 40 years)	-36.5; -19.9
Strategy 2 (WHO PEN guidelines[1])	-43.7; -27.4
Strategy 3 (WHO PEN guidelines[2])	-39.4; -24.7

The uncertainty interval represents 2.5th and 97.5th percentile of the distribution of net health benefits.

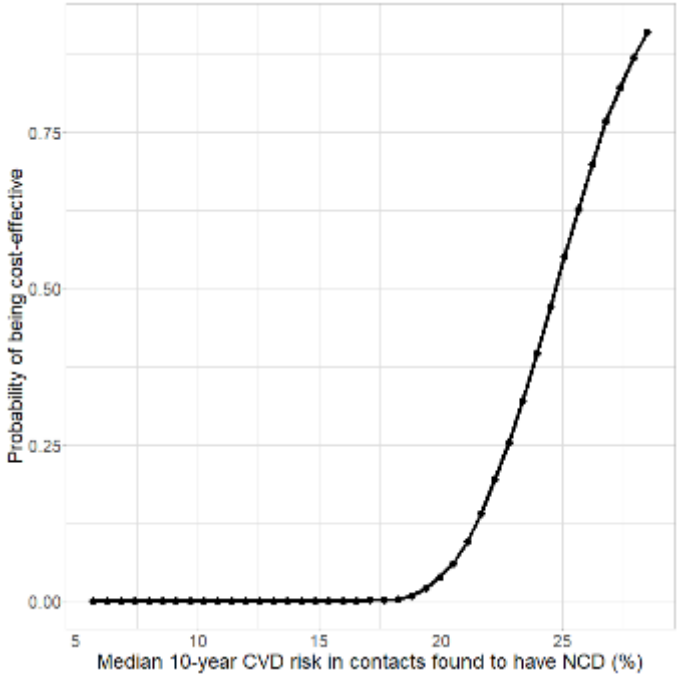
Figure 7-2.Probablistic sensitivity analysis of the cost-effectiveness of integrated NCD screening



Strategy 2: CVD risk assessment and blood pressure measurement in adults aged > 40 years, current smokers, or people who are overweight and testing for diabetes in adults aged > 40 years who are overweight.
Strategy 3: CVD risk assessment and blood pressure measurement in adults aged > 40 years, current smokers, or people who are overweight and testing for diabetes in adults aged > 40 years who are obese.

Figure 7-3 illustrates changes in the probability of the intervention being cost-effective with an increase in the 10-year CVD risk in contacts. When the median risk reached 20%, the probability of being cost-effective started increasing sharply. At a median 10-year CVD risk of 25%, the probability of being cost-effective was 55%.

Figure 7-3.Scenario analysis: Probability of being cost-effective by CVD risk in the population



7.5. Discussion

To my knowledge, this is the first study that evaluated the incremental costs and cost-effectiveness of integrated NCD screening within household contact investigations. The study found an ICER of US$ 24,940.0 per DALY averted, which was above a cost-effectiveness threshold of US$ 3708 per DALY averted in South Africa proposed by Edoka et al.[274] The costs for the management of NCD identified through screening accounted for over 80% of the total incremental costs, resulting in an ICER of US$21257.3 per DALY averted, even when excluding screening costs. This suggests that the cost-effectiveness of integrated NCD screening largely depends on the cost-effectiveness of subsequent care.

Contrary to the findings of this study, Basu et al. reported that scaling up cardiovascular disease treatment in the South African general population—which includes the treatment of hypertension and diabetes, along with statin therapy—

could be cost-saving.[260] Their study also considered additional outcomes, such as renal failure and congestive heart failure due to hypertension, as well as microvascular complications of diabetes (nephropathy, neuropathy, and retinopathy). In contrast, the data available for my study precluded a comprehensive exploration of the impact of CVD treatment across all potential outcomes. Further, my analysis used a simple decision tree model that did not account for recurrent CVD events, even though individuals with prior cardiovascular disease events are at a heightened risk of recurrence.[276] Consequently, the cost-effectiveness observed in my study is likely to be underestimated. In addition, in the study by Basu et al., the 10-year CVD risk in the study population was 9.9% (95% CI: 0-56.0%), which was nearly twice as high as the risk in my cohort (5.7%). This higher CVD risk in their cohort likely contributes to the differences in my findings. In fact, the ICER declined when NCD screening was limited to people aged 40 years and older, who are at a higher risk for CVD. Prioritizing high-risk individuals could enhance the cost-effectiveness of integrated NCD screening strategies. It is also important to consider the goals of South Africa's national strategic plan for NCD 2022-2027, which aims for "90% of all people over 18 will know whether or not they have raised blood pressure and/or raised blood glucose." Given this aim, assuming no treatment of hypertension or diabetes in the baseline scenario may be unrealistic. A comparison against alternative screening methods for these conditions, rather than the absence of screening and treatment, might offer a more realistic scenario.

Integrating NCD screening increased the total provider costs by $71.6, with the most (84%) accounted for by laboratory tests and consumables. HbA1c incurred the highest unit cost ($23.47), followed by total cholesterol ($ 7.82), serum creatinine ($6.85) and blood glucose ($6.85). It should be noted that the present study had a small sample size; scaling up screening with bulk purchasing is expected to reduce the unit costs for these tests as well as the unit costs associated with kit construction and sample transportation. Furthermore, in this study, no diabetes was diagnosed based solely on high random blood glucose levels, and 85% of CKD (eGFR <60 mL/min/1.73m^2) was diagnosed in participants who had diabetes, hypertension, and/or HIV. Therefore, using HbA1c alone for diabetes screening and limiting serum creatinine tests to individuals with comorbidities would further reduce the total costs.

This study has several limitations. First, I did not collect the baseline cost for contact tracing; I only estimated incremental costs for adding NCD screening. Thus, the relative increase in the cost due to the addition of NCD screening is unknown. Second, the cost-effectiveness analysis did not include societal costs, such as productivity losses associated with NCD; their inclusion might have increased the cost-effectiveness. In addition, the analysis did not include patient costs related to receiving NCD care (e.g. clinic waiting time, travel time, and out-of-pocket expenses), though data collected at the initial referral did not suggest them to be substantial. Third, I did not consider losses in the cascade of care. Retention in care is a significant challenge; for instance, a study using the national database in South Africa reported that among people with diabetes, only about 30% of people with diabetes remained in care. Among those who remained in care, only 30% achieved target glycemic control.[277] Suboptimal treatment uptake and retention could undermine the effectiveness of screening activities. Fourth, the study assumed that integrating NCD screening with TB services had no impact on the latter. However, such integration could potentially overburden healthcare workers and compromise the quality of TB care. For example, in the context of household contact investigations, integration might reduce the number of households that can be visited or the number of people who are linked to TB prevention or treatment—though the actual impact remains unknown. Conversely, integration could have beneficial effects, as suggested by the positive outcomes of integrating HIV and other health services.[278]

7.6. Conclusion

In conclusion, the present study did not establish the cost-effectiveness of integrated NCD screening within household contact investigations, potentially influenced by inherent limitations of the methodology used in this economic study. Further, the results need to be interpreted in the context of South Africa's strategic vision for expanding the coverage of NCD treatment and management. The study suggests the potential for improving cost-effectiveness by strategically choosing the types of NCDs screened and by targeting screening efforts toward contacts at high risk. Future cost-effectiveness studies should incorporate empirical data on the impact of integration on both TB and NCD outcomes that can be estimated through

effectiveness trials. Additionally, utilizing microsimulation modelling would enhance the analysis by enabling the modelling of multiple different NCD events occurring over time.

8. Discussion and Conclusions

8.1. Summary of key findings

8.1.1. Association of NCD and NCD risk factors with subclinical-to-symptomatic spectrum of TB

In my IPD meta-analysis of national prevalence surveys, a median proportion of subclinical TB was 38.1% (IQR 25.5- 48.2%) across 16 surveys, where subclinical TB was defined as the absence of any duration of cough, fever, night sweats, and weight loss. This was lower than that reported by a meta-analysis of aggregate data (median: 50.4%, IQR: 39.8%–62.3%),[142] likely because the included studies used various definitions of subclinical TB, including the absence of cough more than two weeks alone +/- other symptoms in some studies.

This IPD meta-analysis identified smoking as a significant risk factor for both symptomatic and subclinical TB. Current smokers were 1.5 times more likely to have either form of TB compared to people who do not currently smoke. While self-reported diabetes also demonstrated an association with symptomatic TB (1.5-fold increased risk), the link with subclinical TB remained inconclusive. Notably, HIV infection exhibited the strongest association, with a 2.2-fold and 2.5-fold increased risk for subclinical and symptomatic TB, respectively. These findings suggest that screening programs could benefit from targeting current smokers and those reporting a history of diabetes, alongside prioritising individuals with HIV. Importantly, self-reported diabetes, even in the absence of confirmatory blood tests, may serve as a valuable tool to identify this high-risk population for TB screening.

8.1.2. Burden of NCD and their determinants in households affected by TB

The IPD meta-analysis of 16 prevalence surveys showed that individuals living in households with TB were more likely to be current smokers (aOR: 1.23, 95% CI 1.11-1.38). The analysis further indicated that current smoking is more prevalent among household members when individuals with TB are also smokers. This suggests that smoking habits tend to cluster within households affected by TB. However, the presence of similar clustering for alcohol consumption and NCD such as diabetes and hypertension was inconclusive, partly due to potential misclassification of NCD status in the absence of objective diagnoses.

Another systematic review and IPD meta-analysis, including contact tracing studies, reviewed four studies that utilised blood tests to identify diabetes and 14 studies based on previously known diabetes diagnoses. This analysis highlighted a lower prevalence of known diabetes among contacts, suggesting a diagnostic gap. When comparing the diabetes prevalence among contacts with their corresponding national prevalence, adjusting for age and gender, there was no clear evidence of a higher prevalence, although point estimates were consistent with a higher prevalence in two of the studies. Data on other NCD were limited, primarily due to the lack of data collection or the absence of objective diagnostic methods.

I subsequently conducted a pilot cross-sectional study in South Africa and Tanzania to assess the burden and patterns of NCD multimorbidity among household contacts. This study employed systematic screening for NCD using blood pressure measurements and blood tests for diabetes, CKD, and total cholesterol. It also compared the NCD prevalence with neighbourhood controls to address the limitations identified in previous meta-analyses. The study found a high prevalence of diabetes and hypertension among contacts, with more than half of these cases newly identified. For instance, the prevalence of diabetes was 12.2% among contacts, including 70% newly diagnosed cases. The large proportion of undiagnosed NCD suggests that integrating NCD screening within contact investigations could provide a platform to identify those who are unaware of their NCD. The comparison with neighbourhood controls showed a similar point prevalence of NCD. However, it should be noted that I could not achieve the target sample size that would provide sufficient power to compare NCD prevalence between the two groups definitively. Hence, it remains inconclusive whether there is a difference in NCD prevalence between the groups.

This pilot study also demonstrated the feasibility of identifying neighbourhood households through a combination of Google satellite images and random coordinates, which can be applied in other studies.

8.1.3. Cost-effectiveness of integrated NCD screening with household contact investigation

In Chapter 7, I explored the incremental costs and cost-effectiveness of integrated NCD screening within household contact investigations. The ICER, expressed as

incremental costs per DALY averted, was $23,568.5, which exceeds the cost-effectiveness threshold in South Africa. The cost-effectiveness analysis focused on CVD outcomes, which might have underestimated the overall cost-effectiveness of NCD screening. Additionally, the evaluation of different targeting strategies revealed that ICER could be improved by limiting the screening to contacts at high risk for CVD. The analysis also indicated that the costs for subsequent management of NCDs detected through screening accounted for the majority (84%) of the incremental costs. These costs are not unique to the integrated screening under evaluation and would likely apply to other NCD screening methods. Given that South Africa aims to increase the coverage of NCD diagnosis and treatment, comparing the costs of integrated screening with other screening approaches may be more appropriate.

8.2. Implications for policy

The high prevalence of undiagnosed hypertension and diabetes suggests the potential benefits of integrating NCD screening with household contact investigation. This approach could facilitate early detection of NCD and prevent associated morbidities. It is also important to address NCD risk factors within households, especially smoking, due to its clustering in households affected by TB and its established association with TB. Addressing smoking would become particularly important if the index person with TB is a smoker. Findings from my study indicate that household members of smokers with TB are more likely to smoke themselves, placing them at a higher risk for both TB and other NCDs. Screening and referral criteria should be tailored according to national policies and goals to decide on whether the intervention is given to all contacts or prioritised to individuals at risk for CVD to enhance cost-effectiveness. In my study, all individuals with a blood pressure above 140 mmHg were assumed to be candidates for drug treatment in accordance with the South African primary care guidelines.[261]In contrast, according to WHO guidelines on CVD management, drug treatment for hypertension in individuals with a CVD risk under 10% is less prioritised unless blood pressure exceeds 160 mmHg. For instance, it might be feasible to offer lifestyle advice at home to individuals with mild hypertension and low CVD risk instead of directly referring them to a clinic.

My pilot clinical study also revealed a high prevalence of NCD among contacts and their neighbourhood controls, with the majority being newly diagnosed through screening. The similar prevalence of NCD between the two groups suggests that people within the same community likely share similar levels of healthcare access and experience similar rates of NCD underdiagnosis. Therefore, extending NCD screening to broader community members might be a reasonable strategy. For example, some studies have suggested that extending contact investigation to neighbourhoods could identify additional people with TB and increase case notification.[279-281] Such a neighbourhood contact investigation could integrate NCD screening to identify individuals who are unaware of their NCD status, given its high prevalence observed in my study. A community-wide integrated screening for TB and NCD could be an alternative strategy. A cluster RCT in Vietnam demonstrated a reduction in TB prevalence through community-wide TB screening.[170] Considering this evidence and others, the WHO recommends systematic screening for TB among the general population in areas with a high TB prevalence, defined as 0.5% or higher. [112] Such screening is resource-intensive, but integrating NCD screening might offer additional benefits by identifying individuals with NCDs, reducing the NCD burden, and subsequently lowering the TB risk. Furthermore, in settings with limited resources, x-ray screening may be prioritized for smokers or those who self-report having diabetes, who are more likely to have TB.

8.3. Knowledge gaps and implications for future research

Table 8-1 summarises the knowledge gaps and implications for future research. Detailed explanations are provided in the text below.

Table 8-1. Knowledge gaps and research implications

Knowledge Gap	Future Research Implications
Acceptability of integrated NCD screening by individuals and healthcare workers	- Conduct qualitative studies to understand household members' views and barriers. - Explore healthcare workers' perspectives on additional screenings and managing NCDs. - Investigate barriers and develop support strategies for programmatic settings.
Impact of NCD screening on TB investigations and developing effective interventions	- Prospectively evaluate the workload impact on TB investigations. - Explore tools (e.g. mHealth tool) to support contact management. - Develop and evaluate smoking cessation interventions integrated with household contact tracing.
Effectiveness of integrated NCD screening	- Evaluate clinical outcomes like mortality, cardiovascular events, and TB incidence through RCTs. - Define outcomes capturing a broad impact of integrated care models on NCDs and other conditions. - Design interventions targeting households or communities and measure outcomes at these levels through cluster RCTs.

Understanding the acceptability of integrated NCD screening by individuals and health care workers

The current study did not evaluate the acceptability of NCD screening among individuals and healthcare workers. A previous qualitative study in South Africa, which involved group interviews with household contacts during home visits, found a demand for diabetes and hypertension screening alongside TB screening.[282] However, there is a lack of data among household contacts who actually received the integrated NCD screening. In my study, among 233 adult household contacts identified, 30 (12.9%) declined screening. This underscores the need for qualitative studies, such as interviews and focus group discussions, to understand household members' views towards integrated NCD screening and to identify barriers and potential solutions.

Acceptability and feasibility from the healthcare workers' perspective are also crucial. It is essential to understand their views on undertaking additional screenings in households and their readiness to manage individuals newly diagnosed with NCDs in clinics. Qualitative studies could provide insights into the barriers to implementing integrated NCD screening and strategies for support in programmatic settings.

Understanding the impact of NCD screening on the existing TB investigation and developing effective interventions

It is also important to evaluate the potential negative effects of the additional workload from NCD screening on TB investigations. Indicators such as the number of households visited, contacts screened, and uptake of TPT under integrated care should be prospectively evaluated. Additionally, evaluating and managing NCD adds complexity to clinical care; factors like smoking history, blood pressure, and age must be considered in care decisions. Using mHealth can facilitate the delivery of NCD care by community healthcare workers, as suggested by previous trials. [283,284] Similarly, the use of mHealth tools to support the management of contacts needs to be explored.

My study identified a clustering of smoking, a significant risk factor for both TB and NCD. However, the best intervention to help smoking cessation integrated within household contact tracing remains unclear. A 2021 scoping review of tobacco cessation in LMIC found four RCTs in South Africa that implemented a range of interventions—behavioural, pharmacological, and psychological—all of which significantly improved cessation rates.[285] One of them introduced brief motivational interviewing by lay healthcare workers to people with TB, which resulted in a higher rate of tobacco abstinence at six months (21.5% vs. 9.3%).[286] Such an approach could potentially be adapted for use in household interventions, but further evaluation is necessary.

Evaluating the effectiveness of integrated NCD screening

While integrated screening is likely to identify additional individuals with NCD, there is a gap in data regarding its impact on critical clinical outcomes such as mortality, CVD events, and incident TB. For example, the recent RATIONS trial demonstrated that providing nutritional supplementation to household contacts significantly reduced TB incidence.[137] Similarly, screening for and treating diabetes among household contacts may reduce TB incidence, but this hypothesis requires evaluation in RCTs. Likewise, the impact of NCD screening on outcomes like CVD events and NCD-related mortality also demands examination. Although early diagnosis and treatment of NCD are presumed to prevent complications, screening alone may not lead to

significant clinical outcomes, particularly if follow-up care and patient retention are inadequate.

Moreover, while existing research on integrated care models primarily focuses on TB outcomes, adopting a broader perspective that encompasses NCD and potentially other conditions is crucial. For instance, interventions like enhanced nutrition (as seen in the RATION trial) or diabetes treatment could also reduce morbidity from other infectious diseases. Integrating TB care with managing other diseases might improve TB outcomes and enhance the overall health status of affected populations. Defining appropriate outcomes that fully capture the potential of integrated TB, NCD, and other interventions is essential. Consultation with experts in well-being, health economics, and UHC could be crucial in identifying these outcomes.

Additionally, interventions could be designed to target entire households or communities rather than individuals alone. Consequently, outcomes might be more appropriately measured at the household or community level, depending on the intervention's scope. Thus, it is ideal to evaluate the impact of integrated NCD and TB screening and care through cluster RCTs with households or communities as units of randomization.

8.4. Dissemination

To disseminate the findings of my research, I published my work in peer-reviewed journals as follows:

- **Introduction:** Hamada, Y., Fong, C. J., Copas, A., Hurst, J. R., & Rangaka, M. X. (2021). Risk for development of active tuberculosis in patients with chronic airway disease-a systematic review of evidence.. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. doi:10.1093/trstmh/trab122

- **Chapter 3:** Hamada, Y., Quartagno, M., Law, I., Malik, F., Bonsu, F. A., Adetifa, I. M. O., . . . Rangaka, M. X. (2024). Tobacco smoking clusters in households affected by tuberculosis in an individual participant data meta-analysis of national tuberculosis prevalence surveys: Time for household-wide interventions?. *PLOS Global Public Health*, *4*(2). doi:10.1371/journal.pgph.0002596

- **Chapter 4:** Hamada, Y., Quartagno, M., Law, I., Malik, F., Bonsu, F. A., Adetifa, I. M. O., . . . Rangaka, M. X. (2023). Association of diabetes, smoking, and alcohol use with subclinical-to-symptomatic spectrum of tuberculosis in 16 countries: an individual participant data meta-analysis of national tuberculosis prevalence surveys. eClinicalMedicine, 63. doi:10.1016/j.eclinm.2023.102191

- **Chapter 5:** Hamada, Y., Quartagno, Malik, F., . . . Rangaka, M. X. (2024). Prevalence of non-communicable diseases among household contacts of people with tuberculosis: a systematic review and individual participant data meta-analysis. Tropical Medicine & International Health. *In press*.

- **Chapter 6:** Hamada Y, Lugendo A, Ntshiqa T, … Rangaka, M. X. A pilot cross-sectional study of non-communicable diseases in TB household contacts. IJTLD OPEN 2024; 1(4): 154-9. doi: https://doi.org/10.5588/ijtldopen.23.0579

Additionally, I gave the following conference presentations:

- Prevalence of non-communicable diseases among household contacts of microbiologically confirmed pulmonary TB patients in Gauteng Province, South Africa. Poster presentation at the South African TB Conference. Durban, South Africa. 2023.

- A Pilot Cross-Sectional Study of Non-Communicable Diseases in TB Household Contacts in South Africa and Tanzania. Poster presentation at the South African TB Conference. Durban, South Africa. 2024.

- Design of multifaceted clinical and socio-economic interventions for TB and associated NCD comorbidity in households affected by tuberculosis and in the community. Poster presentation at the Regional Non-Communicable Diseases Scientific Conference. Dar es Salaam, Tanzania. 2023

Furthermore, I organized two webinars inviting national TB program managers and WHO country officers from 16 countries as well as WHO technical officers at the headquarters to share findings from my research. In addition, I plan to organize a webinar in early 2025, in collaboration with researchers at the London School of Hygiene and Tropical Medicine, to review recent research findings on the multiple

impacts of TB on members of affected households and highlight the need for supporting person-centred TB screening programs.

Lastly, following the findings from my PhD research, I plan to apply for a fellowship to undertake a trial to evaluate the effectiveness of integrated NCD and TB screening and care delivered to TB-affected households, which will further enhance the impact of my work.

8.5. Conclusion

This thesis has examined the interplay between TB and key TB-associated NCD and risk factors in households affected by TB in LMIC. My findings have demonstrated a high prevalence of subclinical TB and its association with NCD-related factors like smoking and self-reported diabetes, reinforcing the necessity for targeted screening strategies that include these high-risk groups. Moreover, systematic reviews and a clinical study in South Africa and Tanzania have shown the substantial burden of undiagnosed NCDs, particularly diabetes and hypertension, within these households and in the neighbouring community, underscoring the value of integrated screening programs.

Integrating NCD screening within TB contact investigations may facilitate the early detection of NCD and offer a strategic point of intervention that could substantially mitigate the dual burden of disease in affected populations. Although the cost-effectiveness of such integrated screening was found to exceed the willingness-to-pay threshold in South Africa, strategic adjustments and targeted approaches could optimize cost-effectiveness. This approach should be considered in the context of national health priorities and its potential for improving overall health outcomes. Policy implications derived from this work advocate for the implementation of integrated TB-NCD screening to capitalize on contact investigations as a platform for broader health interventions. However, gaps remain in our understanding of TB-NCD multimorbidity. Future research should aim to fill these gaps, particularly through qualitative studies that assess the acceptability and feasibility of integrated screening programs and randomised controlled trials to evaluate their impact on broader health and social outcomes at the household level or beyond. This thesis sets the stage for deriving and evaluating person-centred interventions delivered to households and communities affected by TB in LMIC.

9. References

1. World Health Organization. Global TB Report, 2023. Geneva, Switzerland: WHO, 2023. https://www.who.int/publications/i/item/9789240083851 Accessed 7 May 2024).
2. Silva S, Arinaminpathy N, Atun R, Goosby E, Reid M. Economic impact of tuberculosis mortality in 120 countries and the cost of not achieving the Sustainable Development Goals tuberculosis targets: a full-income analysis. *The Lancet Global Health* 2021; **9**(10): e1372-e9.
3. World Health Organization. Implementing the end TB strategy: the essentials. Geneva, Switzerland: WHO, 2015. https://www.who.int/tb/publications/2015/end_tb_essential.pdf (accessed 20 December 2021).
4. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020. Available from http://ghdx.healthdata.org/gbd-results-tool. [Accessed 29 April 2022].
5. Bollyky TJ, Templin T, Cohen M, Dieleman JL. Lower-Income Countries That Face The Most Rapid Shift In Noncommunicable Disease Burden Are Also The Least Prepared. *Health affairs (Project Hope)* 2017; **36**(11): 1866-75.
6. World Health Organization. Noncommunicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases [Accessed 22 August 2023].
7. World Health Organization and World Economic Forum. From Burden to "Best Buys": Reducing the Economic Impact of Non-Communicable Disease in Low and Middle-Income Countries. 2011. https://www.who.int/nmh/publications/best_buys_summary.pdf accessed 20 December 2021.
8. Bennett JE, Kontis V, Mathers CD, et al. NCD Countdown 2030: pathways to achieving Sustainable Development Goal target 3.4. *The Lancet* 2020; **396**(10255): 918-34.
9. ATS/CDC. Targeted Tuberculin Testing andTreatment of Latent TB infection. MMWR 2000; 49 (No.RR-6) https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm.
10. National Institute for Health and Care Excellence. Tuberculosis: prevention, diagnosis, management and service organisation (NICE guideline 33). 2016. www.nice.org.uk/guidance/ng33.
11. World Health Organization. Framework for collaborative action on tuberculosis and comorbidities. Geneva: World Health Organization. 2022. https://www.who.int/publications/i/item/9789240055056 (accessed 10 August 2023).
12. Hayashi S, Chandramohan D. Risk of active tuberculosis among people with diabetes mellitus: systematic review and meta-analysis. *Trop Med Int Health* 2018; **23**(10): 1058-70.
13. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLoS One* 2017; **12**(11): e0187967.
14. Kumar Nathella P, Babu S. Influence of diabetes mellitus on immunity to human tuberculosis. *Immunology* 2017; **152**(1): 13-24.

15. Liu Q, Yan W, Liu R, Bo E, Liu J, Liu M. The Association Between Diabetes Mellitus and the Risk of Latent Tuberculosis Infection: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2022; **9**: 899821.
16. Restrepo BI. Diabetes and Tuberculosis. *Microbiology Spectrum* 2016; **4**(6): 10.1128/microbiolspec.tnmi7-0023-2016.
17. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2019; **23**(7): 783-96.
18. Noubiap JJ, Nansseu JR, Nyaga UF, et al. Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2.3 million patients with tuberculosis. *The Lancet Global Health* 2019; **7**(4): e448-e60.
19. Romanowski K, Clark EG, Levin A, Cook VJ, Johnston JC. Tuberculosis and chronic kidney disease: an emerging global syndemic. *Kidney Int* 2016; **90**(1): 34-40.
20. Al-Efraij K, Mota L, Lunny C, Schachter M, Cook V, Johnston J. Risk of active tuberculosis in chronic kidney disease: a systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease* 2015; **19**(12): 1493-9.
21. World Health Organization. WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva, Switzerland: WHO, 2020.
22. Luczynski P, Holmes T, Romanowski K, et al. Risk of Tuberculosis Disease in People With Chronic Kidney Disease Without Kidney Failure: A Systematic Review and Meta-analysis. *Clinical Infectious Diseases* 2023.
23. Cheng MP, Abou Chakra CN, Yansouni CP, et al. Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. *Clin Infect Dis* 2017; **64**(5): 635-44.
24. Dobler CC, Cheung K, Nguyen J, Martin A. Risk of tuberculosis in patients with solid cancers and haematological malignancies: a systematic review and meta-analysis. *The European respiratory journal* 2017; **50**(2).
25. Chai M, Shi Q. The effect of anti-cancer and anti-tuberculosis treatments in lung cancer patients with active tuberculosis: a retrospective analysis. *BMC Cancer* 2020; **20**(1): 1121.
26. Ye MF, Su S, Huang ZH, et al. Efficacy and safety of concurrent anti-tuberculosis treatment and chemotherapy in lung cancer patients with co-existent tuberculosis. *Ann Transl Med* 2020; **8**(18): 1143.
27. Ehrlich R, Akugizibwe P, Siegfried N, Rees D. The association between silica exposure, silicosis and tuberculosis: a systematic review and meta-analysis. *BMC Public Health* 2021; **21**(1): 953.
28. Hamada Y, Fong CJ, Copas A, Hurst JR, Rangaka MX. Risk for development of active tuberculosis in patients with chronic airway disease-a systematic review of evidence. *Trans R Soc Trop Med Hyg* 2021.
29. O'Toole RF, Shukla SD, Walters EH. TB meets COPD: An emerging global co-morbidity in human lung disease. *Tuberculosis (Edinburgh, Scotland)* 2015; **95**(6): 659-63.
30. Inghammar M, Ekbom A, Engstrom G, et al. COPD and the risk of tuberculosis--a population-based cohort study. *PLoS ONE [Electronic Resource]* 2010; **5**(4): e10138.
31. Attia EF, McGinnis KA, Feemster LC, et al. Association of COPD With Risk for Pulmonary Infections Requiring Hospitalization in HIV-Infected Veterans. *Journal of Acquired Immune Deficiency Syndromes: JAIDS* 2015; **70**(3): 280-8.

32. Duko B, Bedaso A, Ayano G. The prevalence of depression among patients with tuberculosis: a systematic review and meta-analysis. *Ann Gen Psychiatry* 2020; **19**: 30.
33. Courtwright A, Turner AN. Tuberculosis and stigmatization: pathways and interventions. *Public Health Rep* 2010; **125 Suppl 4**(Suppl 4): 34-42.
34. Baral SC, Aryal Y, Bhattrai R, King R, Newell JN. The importance of providing counselling and financial support to patients receiving treatment for multi-drug resistant TB: mixed method qualitative and pilot intervention studies. *BMC Public Health* 2014; **14**(1): 46.
35. Hayward SE, Deal A, Rustage K, et al. The relationship between mental health and risk of active tuberculosis: a systematic review. *BMJ open* 2022; **12**(1): e048945.
36. Lee G, Scuffell J, Galea JT, et al. Impact of mental disorders on active TB treatment outcomes: a systematic review and meta-analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2020; **24**(12): 1279-84.
37. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med* 2019; **25**(12): 1822-32.
38. Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nature Reviews Endocrinology* 2021; **17**(1): 11-30.
39. Magee MJ, Salindri AD, Gujral UP, et al. Convergence of non-communicable diseases and tuberculosis: a two-way street? *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2018; **22**(11): 1258-68.
40. Menon S, Rossi R, Dusabimana A, Zdraveska N, Bhattacharyya S, Francis J. The epidemiology of tuberculosis-associated hyperglycemia in individuals newly screened for type 2 diabetes mellitus: systematic review and meta-analysis. *BMC Infect Dis* 2020; **20**(1).
41. Pearson F, Huangfu P, McNally R, Pearce M, Unwin N, Critchley JA. Tuberculosis and diabetes: bidirectional association in a UK primary care data set. *J Epidemiol Community Health* 2019; **73**(2): 142-7.
42. Magee MJ, Khakharia A, Gandhi NR, et al. Increased Risk of Incident Diabetes Among Individuals With Latent Tuberculosis Infection. *Diabetes Care* 2022; **45**(4): 880-7.
43. Wongtrakul W, Charoenngam N, Ungprasert P. Tuberculosis and risk of coronary heart disease: A systematic review and meta-analysis. *Indian J Tuberc* 2020; **67**(2): 182-8.
44. Sumbal A, Sheikh SM, Ikram A, Amir A, Sumbal R, Saeed AR. Latent Tuberculosis Infection (LTBI) as a predictor of coronary artery disease: A systematic review and meta-analysis. *Heliyon* 2023; **9**(4): e15365.
45. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. *European Respiratory Review* 2018; **27**(147): 170077.
46. Fan H, Wu F, Liu J, et al. Pulmonary tuberculosis as a risk factor for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Annals of Translational Medicine* 2021; **9**(5): 390-.
47. Taylor J, Bastos ML, Lachapelle-Chisholm S, Mayo NE, Johnston J, Menzies D. Residual respiratory disability after successful treatment of pulmonary tuberculosis: a systematic review and meta-analysis. *EClinicalMedicine* 2023; **59**: 101979.
48. van Kampen SC, Jones R, Kisembo H, et al. Chronic Respiratory Symptoms and Lung Abnormalities Among People With a History of Tuberculosis in Uganda: A National Survey. *Clin Infect Dis* 2019; **68**(11): 1919-25.

49. Cabrera-Sanchez J, Cuba V, Vega V, Van der Stuyft P, Otero L. Lung cancer occurrence after an episode of tuberculosis: a systematic review and meta-analysis. *Eur Respir Rev* 2022; **31**(165).
50. Quan DH, Kwong AJ, Hansbro PM, Britton WJ. No smoke without fire: the impact of cigarette smoking on the immune control of tuberculosis. *European Respiratory Review* 2022; **31**(164): 210252.
51. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Archives of internal medicine* 2007; **167**(4): 335-42.
52. Lin H-H, Ezzati M, Murray M. Tobacco Smoke, Indoor Air Pollution and Tuberculosis: A Systematic Review and Meta-Analysis. *PLoS Med* 2007; **4**(1): e20.
53. Slama K, Chiang CY, Enarson DA, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis [Review Article]. *The International Journal of Tuberculosis and Lung Disease* 2007; **11**(10): 1049-61.
54. Vidyasagaran AL, Readshaw A, Boeckmann M, et al. Is Tobacco Use Associated With Risk of Recurrence and Mortality Among People With TB?: A Systematic Review and Meta-Analysis. *Chest* 2023.
55. Patra J, Bhatia M, Suraweera W, et al. Exposure to Second-Hand Smoke and the Risk of Tuberculosis in Children and Adults: A Systematic Review and Meta-Analysis of 18 Observational Studies. *PLoS Med* 2015; **12**(6): e1001835.
56. Dogar OF, Pillai N, Safdar N, Shah SK, Zahid R, Siddiqi K. Second-hand smoke and the risk of tuberculosis: a systematic review and a meta-analysis. *Epidemiol Infect* 2015; **143**(15): 3158-72.
57. https://ncdalliance.org/why-ncds/risk-factors-prevention/tobacco-use.
58. Dai X, Gil GF, Reitsma MB, et al. Health effects associated with smoking: a Burden of Proof study. *Nat Med* 2022; **28**(10): 2045-55.
59. Reitsma MB, Kendrick PJ, Ababneh E, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *The Lancet* 2021; **397**(10292): 2337-60.
60. https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health.
61. Lee KK, Bing R, Kiang J, et al. Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study. *Lancet Glob Health* 2020; **8**(11): e1427-e34.
62. Dimala CA, Kadia BM. A systematic review and meta-analysis on the association between ambient air pollution and pulmonary tuberculosis. *Sci Rep* 2022; **12**(1): 11282.
63. Schraufnagel DE, Balmes JR, Cowl CT, et al. Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems. *Chest* 2019; **155**(2): 417-26.
64. https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health.
65. https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
66. Hamada Y, Getahun H, Tadesse BT, Ford N. HIV-associated tuberculosis. *Int J STD AIDS* 2021; **32**(9): 780-90.
67. So-Armah K, Benjamin LA, Bloomfield GS, et al. HIV and cardiovascular disease. *The Lancet HIV* 2020; **7**(4): e279-e93.

68. Eyawo O, Brockman G, Goldsmith CH, et al. Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis. *BMJ open* 2019; **9**(9): e025874.
69. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV* 2017; **4**(11): e495-e504.
70. Swanepoel CR, Atta MG, D'Agati VD, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2018; **93**(3): 545-59.
71. Fahme SA, Bloomfield GS, Peck R. Hypertension in HIV-Infected Adults: Novel Pathophysiologic Mechanisms. *Hypertension* 2018; **72**(1): 44-55.
72. Sarkar S, Brown TT. Diabetes in People with HIV. *Curr Diab Rep* 2021; **21**(5): 13.
73. Moyo-Chilufya M, Maluleke K, Kgarosi K, Muyoyeta M, Hongoro C, Musekiwa A. The burden of non-communicable diseases among people living with HIV in Sub-Saharan Africa: a systematic review and meta-analysis. *eClinicalMedicine* 2023; **65**.
74. World Health Organization. Global strategy to reduce the harmful use of alcohol. Geneva: World Health Organization. 2010. https://www.who.int/publications/i/item/9789241599931 (accessed 26 October 2023).
75. Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis – a systematic review. *BMC Public Health* 2008; **8**(1): 289.
76. Simou E, Britton J, Leonardi-Bee J. Alcohol consumption and risk of tuberculosis: a systematic review and meta-analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2018; **22**(11): 1277-85.
77. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *The European respiratory journal* 2017; **50**(1): 1700216.
78. Ragan EJ, Kleinman MB, Sweigart B, et al. The impact of alcohol use on tuberculosis treatment outcomes: a systematic review and meta-analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2020; **24**(1): 73-82.
79. Weiangkham D, Umnuaypornlert A, Saokaew S, Prommongkol S, Ponmark J. Effect of alcohol consumption on relapse outcomes among tuberculosis patients: A systematic review and meta-analysis. *Front Public Health* 2022; **10**: 962809.
80. Shield K, Manthey J, Rylett M, et al. National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: a comparative risk assessment study. *The Lancet Public Health* 2020; **5**(1): e51-e61.
81. https://www.who.int/news-room/questions-and-answers/item/malnutrition.
82. Lönnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010-2050: cure, care, and social development. *The Lancet* 2010; **375**(9728): 1814-29.
83. Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. *Int J Epidemiol* 2009; **39**(1): 149-55.
84. Cho SH, Lee H, Kwon H, et al. Association of underweight status with the risk of tuberculosis: a nationwide population-based cohort study. *Sci Rep* 2022; **12**(1): 16207.
85. MacAllan DC, McNurlan MA, Kurpad AV, et al. Whole Body Protein Metabolism in Human Pulmonary Tuberculosis and Undernutrition: Evidence for Anabolic Block in Tuberculosis. *Clin Sci* 1998; **94**(3): 321-31.

86. Badawi A, Gregg B, Vasileva D. Systematic analysis for the relationship between obesity and tuberculosis. *Public Health* 2020; **186**: 246-56.
87. Wagnew F, Alene KA, Kelly M, Gray D. The effect of undernutrition on sputum culture conversion and treatment outcomes among people with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Infect Dis* 2023; **127**: 93-105.
88. Lin HH, Wu CY, Wang CH, et al. Association of Obesity, Diabetes, and Risk of Tuberculosis: Two Population-Based Cohorts. *Clin Infect Dis* 2018; **66**(5): 699-705.
89. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol* 2018; **6**(12): 944-53.
90. Kivimaki M, Strandberg T, Pentti J, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. *Lancet Diabetes Endocrinol* 2022; **10**(4): 253-63.
91. Pati S, Irfan W, Jameel A, Ahmed S, Shahid RK. Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers (Basel)* 2023; **15**(2).
92. Chong B, Jayabaskaran J, Kong G, et al. Trends and predictions of malnutrition and obesity in 204 countries and territories: an analysis of the Global Burden of Disease Study 2019. *EClinicalMedicine* 2023; **57**: 101850.
93. Theilmann M, Lemp JM, Winkler V, et al. Patterns of tobacco use in low and middle income countries by tobacco product and sociodemographic characteristics: nationally representative survey data from 82 countries. *BMJ* 2022; **378**: e067582.
94. Allen LN, Townsend N, Williams J, Mikkelsen B, Roberts N, Wickramasinghe K. Socioeconomic status and alcohol use in low- and lower-middle income countries: A systematic review. *Alcohol* 2018; **70**: 23-31.
95. Allen L, Williams J, Townsend N, et al. Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. *Lancet Glob Health* 2017; **5**(3): e277-e89.
96. Siroka A, Ponce NA, Lönnroth K. Association between spending on social protection and tuberculosis burden: a global analysis. *Lancet Infect Dis* 2016; **16**(4): 473-9.
97. Stringhini S, Bovet P. Socioeconomic status and risk factors for non-communicable diseases in low-income and lower-middle-income countries. *The Lancet Global Health* 2017; **5**(3): e230-e1.
98. Seiglie JA, Marcus ME, Ebert C, et al. Diabetes Prevalence and Its Relationship With Education, Wealth, and BMI in 29 Low- and Middle-Income Countries. *Diabetes Care* 2020; **43**(4): 767-75.
99. Kirschbaum TK, Sudharsanan N, Manne-Goehler J, et al. The Association of Socioeconomic Status With Hypertension in 76 Low- and Middle-Income Countries. *J Am Coll Cardiol* 2022; **80**(8): 804-17.
100. Antignac M, Diop IB, Terline DMd, et al. Socioeconomic Status and Hypertension Control in Sub-Saharan Africa. *Hypertension* 2018; **71**(4): 577-84.
101. COVID-19 epidemiological update – 17 June 2024 Edition 168. https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-168.
102. https://covid19.who.int/ Accessed 29 November 2023.
103. World Health Organization. Presentation of Preliminary Results of 2021 Assessment on NCD Service Disruption during COVID-19 Pandemic. 2021 (accessed 8 February 2022.

104. Chiok KR, Dhar N, Banerjee A. Mycobacterium tuberculosis and SARS-CoV-2 co-infections: The knowns and unknowns. *iScience* 2023; **26**(5): 106629.
105. Kumwichar P, Chongsuvivatwong V. COVID-19 pneumonia and the subsequent risk of getting active pulmonary tuberculosis: a population-based dynamic cohort study using national insurance claims databases. *eClinicalMedicine* 2023; **56**.
106. Nikoloski Z, Alqunaibet AM, Alfawaz RA, et al. Covid-19 and non-communicable diseases: evidence from a systematic literature review. *BMC Public Health* 2021; **21**(1): 1068.
107. World Health, Organization, United Nations Development, Programme. Responding to non-communicable diseases during and beyond the COVID-19 pandemic: state of the evidence on COVID-19 and non-communicable diseases: a rapid review. CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization, 2020.
108. Gordon Patti K, Kohli P. COVID's Impact on Non-communicable Diseases: What We Do Not Know May Hurt Us. *Curr Cardiol Rep* 2022; **24**(7): 829-37.
109. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; **28**(3): 583-90.
110. Ssentongo P, Zhang Y, Witmer L, Chinchilli VM, Ba DM. Association of COVID-19 with diabetes: a systematic review and meta-analysis. *Sci Rep* 2022; **12**(1): 20191.
111. WHO Regional Office for Europe. Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm.
Copenhagen: Copenhagen, Denmark: WHO Regional Office for Europe, 2020.
112. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease.
https://apps.who.int/iris/bitstream/handle/10665/340255/9789240022676-eng.pdf (accessed 11 January 2023).
113. Fox GJ, Nhung NV, Sy DN, et al. Household-Contact Investigation for Detection of Tuberculosis in Vietnam. *New England Journal of Medicine* 2018; **378**(3): 221-9.
114. World Health Organization. Implementing the end TB strategy: the essentials, 2022 update. Geneva: World Health Organization. 2022.
https://www.who.int/publications/i/item/9789240065093 (accessed 10 August 2023).
115. *Nigeria Bureau of Statistics https://nigerianstatgovng/elibrary/read/1123 Accessed 16 November 2023*.
116. Armstrong-Hough M, Turimumahoro P, Meyer AJ, et al. Drop-out from the tuberculosis contact investigation cascade in a routine public health setting in urban Uganda: A prospective, multi-center study. *PLoS One* 2017; **12**(11): e0187145.
117. Szkwarko D, Hirsch-Moverman Y, Du Plessis L, Du Preez K, Carr C, Mandalakas AM. Child contact management in high tuberculosis burden countries: A mixed-methods systematic review. *PLoS One* 2017; **12**(8): e0182185.
118. Bonnet M, Vasiliu A, Tchounga BK, et al. Effectiveness of a community-based approach for the investigation and management of children with household tuberculosis contact in Cameroon and Uganda: a cluster-randomised trial. *Lancet Glob Health* 2023.
119. Global report on hypertension: the race against a silent killer. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.
120. Schutte AE, Venkateshmurthy NS, Mohan S, Prabhakaran D. Hypertension in Low- and Middle-Income Countries. *Circ Res* 2021; **128**(7): 808-26.

121. WHO package of essential noncommunicable (PEN) disease interventions for primary health care: WHO, 2020. https://www.who.int/publications/i/item/9789240009226 (accessed 23 May 2024).
122. Flood D, Seiglie JA, Dunn M, et al. The state of diabetes treatment coverage in 55 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 680 102 adults. *The Lancet Healthy Longevity* 2021; **2**(6): e340-e51.
123. Teufel F, Seiglie JA, Geldsetzer P, et al. Body-mass index and diabetes risk in 57 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 685 616 adults. *Lancet* 2021; **398**(10296): 238-48.
124. World Health Organization. HEARTS technical package for cardiovascular disease management in primary health care: risk based CVD management; 2020. https://iris.who.int/bitstream/handle/10665/333221/9789240001367-eng.pdf?sequence=1 (accessed 25 September 2023).
125. Marcus ME, Manne-Goehler J, Theilmann M, et al. Use of statins for the prevention of cardiovascular disease in 41 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data. *Lancet Glob Health* 2022; **10**(3): e369-e79.
126. United Nations General Assembly. 66th session, 'Political declaration of the high-level meeting of the general assembly on the prevention and control of non-communicable diseases: resolution/adopted by the general assembly'. 2012. Available: https://digitallibrary.un.org/record/720106?ln=en.
127. United Nations General Assembly, 73rd session, 'Political declaration of the 3rd high-level meeting of the general assembly on the prevention and control of non-communicable diseases: resolution/adopted by the general assembly'. 2018. Available: https://digitallibrary.un.org/record/1648984?ln=en.
128. Tracking universal health coverage: 2023 global monitoring report. Geneva: World Health Organization and International Bank for Reconstruction and Development / The World Bank; 2023. Licence: CC BY-NC-SA 3.0 IGO.
129. Integrating the prevention and control of noncommunicable diseases in HIV/AIDS, tuberculosis, and sexual and reproductive health programmes: implementation guidance. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.
130. McCombe G, Lim J, Hout MCV, et al. Integrating Care for Diabetes and Hypertension with HIV Care in Sub-Saharan Africa: A Scoping Review. *Int J Integr Care* 2022; **22**(1): 6.
131. World Health Organization. Collaborative Framework for Care and Control of Tuberculosis and Diabetes. Geneva: World Health Organization; 2011. https://apps.who.int/iris/bitstream/handle/10665/44698/9789241502252_eng.pdf?sequence=1&isAllowed=y (accessed 23 May 2024).
132. World Health Organization. Guideline: Nutritional care and support for patients with tuberculosis. Geneva: World Health Organization; 2013. https://apps.who.int/iris/bitstream/handle/10665/94836/9789241506410_eng.pdf (accessed 25 December 2021).
133. Creswell J, Raviglione M, Ottmani S, et al. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities. *The European respiratory journal* 2011; **37**(5): 1269-82.

134. Law I, Floyd K, Group tATPS. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. *Trop Med Int Health* 2020; **25**(11): 1308-27.
135. StopTB Field guide 6: Using Contact Investigation to Improve TB Case Detection. Geneva: Stop TB. 2018 . Available from: https://stoptb-strategicinitiative.org/elearning/wp-content/uploads/2019/04/STBFG_06.pdf [Accessed 25 December 2021].
136. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.. Geneva: World Health Organization; 2013. https://apps.who.int/iris/bitstream/handle/10665/77741/9789241504492_eng.pdf?sequence=1&isAllowed=y (accessed 25 December 2021).
137. Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. *The Lancet* 2023; **402**(10402): 627-40.
138. Qin Y, Guo Y, Tang Y, et al. Concordance of chronic conditions among the household members in Shanghai: a cross-sectional study. *BMJ open* 2019; **9**(12): e031240.
139. Patel SA, Dhillon PK, Kondal D, et al. Chronic disease concordance within Indian households: A cross-sectional study. *PLoS Med* 2017; **14**(9): e1002395.
140. Shivakumar S, Chandrasekaran P, Kumar AMV, et al. Diabetes and pre-diabetes among household contacts of tuberculosis patients in India: is it time to screen them all? *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2018; **22**(6): 686-94.
141. Restrepo BI, Kleynhans L, Salinas AB, et al. Diabetes screen during tuberculosis contact investigations highlights opportunity for new diabetes diagnosis and reveals metabolic differences between ethnic groups. *Tuberculosis* 2018; **113**: 10-8.
142. Frascella B, Richards AS, Sossen B, et al. Subclinical Tuberculosis Disease-A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology. *Clin Infect Dis* 2021; **73**(3): e830-e41.
143. World Health Organization. Tuberculosis prevalence surveys: a handbook. Geneva: World Health Organization; 2013. https://apps.who.int/iris/rest/bitstreams/52944/retrieve (accessed 25 December 2021).
144. World Health Organization. Global TB Report, 2022. Geneva, Switzerland: WHO, 2022. https://apps.who.int/iris/rest/bitstreams/1474924/retrieve [Accessed 20 January 2023].
145. Von Hippel PT. HOW TO IMPUTE INTERACTIONS, SQUARES, AND OTHER TRANSFORMED VARIABLES. *Sociol Methodol* 2009; **39**(1): 265-91.
146. Fox MP, MacLehose RF, Lash TL. Probabilistic Bias Analysis for Simulation of Record-Level Data. Applying Quantitative Bias Analysis to Epidemiologic Data Second Edition. Switzerland: Springer; 2021: 291-326.
147. Ning M, Zhang Q, Yang M. Comparison of self-reported and biomedical data on hypertension and diabetes: findings from the China Health and Retirement Longitudinal Study (CHARLS). *BMJ open* 2016; **6**(1): e009836.
148. Schneider AL, Pankow JS, Heiss G, Selvin E. Validity and reliability of self-reported diabetes in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2012; **176**(8): 738-43.

149. Gonçalves VSS, Andrade KRC, Carvalho KMB, Silva MT, Pereira MG, Galvao TF. Accuracy of self-reported hypertension: a systematic review and meta-analysis. *J Hypertens* 2018; **36**(5): 970-8.
150. Wellman JL, Holmes B, Hill SY. Accuracy of self-reported hypertension: Effect of age, gender, and history of alcohol dependence. *J Clin Hypertens (Greenwich)* 2020; **22**(5): 842-9.
151. Ministry of Health, Republic of Indonesia, National Institute of Health Research And Development In collaboration with Directorate General of Disease Control and Environmental Health, Indonesia Tuberculosis Prevalence Survey 2013-2014, June 2015.
152. Ministry of Health – Mongolia. Report of the First National Tuberculosis Prevalence Survey in Mongolia 2014-2015. Ulaanbaatar City, Mongolia, 2016.
153. Department of Health- Philippines. National Tuberculosis Prevalence Survey 2016.
154. Ghana Health Service. Ghanaian National Population Based Tuberculosis Prevalence Survey in 2013. Accra, Ghana, 2015.
155. Ministry of Health and Social Services - Republic of Namibia. Namibia Tuberculosis Disease Prevalence Survey Report. 2018.
156. Ministry of Health and Social Welfare – Tanzania. The First National Tuberculosis Prevalence Survey in the United Republic of Tanzania, Final Report. 2013.
157. Ministry of Health - Eswatini. The National TB Prevalence Survey. 2018.
158. Federal Republic of Nigeria. Report: First National TB Prevalence Survey. 2012.
159. National Tuberculosis Control Programme (NTP), Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare. National Tuberculosis Prevalence Survey, Bangladesh 2015-2016.
160. Ministry of Health. National Tuberculosis Prevalence Survey, Lesotho, 2021.
161. Ministry of Health National TB Control Programme. Technical report: Malawi tuberculosis prevalence survey (2013–2014). 2016.
162. Ministry of Health and Social Welfare. The Gambian Survey of Tuberculosis Prevalence Report. Medical Research Council Unit: The Gambia, 2014.
163. Makerere University School of Public Health. Ministry of Health Uganda and Makerere University School of Public Health. Population-based survey of prevalence of tuberculosis disease in Uganda 2014–15 (report). Makerere University School of Public Health: Kampala, Uganda, 2016.
164. Department of Health. The First National TB Prevalence Survey South Africa 2018.
165. REPÚBLICA DE MOÇAMBIQUE MINISTÉRIO DA SAÚDE DIRECÇÃO NACIONAL DE SAÚDE PÚBLICA INSTITUTO NACIONAL DE SAÚDE. The First National Pulmonary Tuberculosis Prevalence Survey in Mozambique. Report Augut 2021.
166. Nguyen HV, Tiemersma EW, Nguyen HB, et al. The second national tuberculosis prevalence survey in Vietnam. *PLoS One* 2020; **15**(4): e0232142.
167. Datiko DG, Guracha EA, Michael E, et al. Sub-national prevalence survey of tuberculosis in rural communities of Ethiopia. *BMC Public Health* 2019; **19**(1): 295.
168. Dhanaraj B, Papanna MK, Adinarayanan S, et al. Prevalence and risk factors for adult pulmonary tuberculosis in a metropolitan city of South India. *PLoS One* 2015; **10**(4): e0124260.
169. Thomas BE, Thiruvengadam K, Vedhachalam C, et al. Prevalence of pulmonary tuberculosis among the tribal populations in India. *PLoS One* 2021; **16**(6): e0251519.
170. Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New England Journal of Medicine* 2019; **381**(14): 1347-57.

171. Gunasekera K, Cohen T, Gao W, Ayles H, Godfrey-Faussett P, Claassens M. Smoking and HIV associated with subclinical tuberculosis: analysis of a population-based prevalence survey. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2020; **24**(3): 340-6.
172. Di Castelnuovo A, Quacquaruccio G, Donati MB, de Gaetano G, Iacoviello L. Spousal concordance for major coronary risk factors: a systematic review and meta-analysis. *Am J Epidemiol* 2009; **169**(1): 1-8.
173. Venters MH, Jacobs DR, Jr., Luepker RV, Maiman LA, Gillum RF. Spouse concordance of smoking patterns: the Minnesota Heart Survey. *Am J Epidemiol* 1984; **120**(4): 608-16.
174. Lee PH, Fu H, Lai TC, Chiang CY, Chan CC, Lin HH. Glycemic Control and the Risk of Tuberculosis: A Cohort Study. *PLoS medicine* 2016; **13**(8): e1002072.
175. Riley L, Guthold R, Cowan M, et al. The World Health Organization STEPwise Approach to Noncommunicable Disease Risk-Factor Surveillance: Methods, Challenges, and Opportunities. *Am J Public Health* 2016; **106**(1): 74-8.
176. Indian Council of Medical Research. Central TB Division, Ministry of Health and Family Welfare, Government of India, National TB prevalence survey in India. https://tbcindia.mohfw.gov.in/wp-content/uploads/2023/05/25032022161020NATBPSReport.pdf.
177. Ray CS, Pednekar MS, Gupta PC, Bansal-Travers M, Quah A, Fong GT. Social impacts on adult use of tobacco: findings from the International Tobacco Control Project India, Wave 1 Survey. *WHO South East Asia J Public Health* 2016; **5**(2): 123-32.
178. Miller CR, Mitchell EMH, Nishikiori N, Zwerling A, Lönnroth K. ScreenTB: a tool for prioritising risk groups and selecting algorithms for screening for active tuberculosis. *The International Journal of Tuberculosis and Lung Disease* 2020; **24**(4): 367-75.
179. Obore N, Kawuki J, Guan J, Papabathini SS, Wang L. Association between indoor air pollution, tobacco smoke and tuberculosis: an updated systematic review and meta-analysis. *Public Health* 2020; **187**: 24-35.
180. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data: The PRISMA-IPD Statement. *JAMA* 2015; **313**(16): 1657-65.
181. Stuck L, van Haaster A-C, Kapata-Chanda P, Klinkenberg E, Kapata N, Cobelens F. How “Subclinical” is Subclinical Tuberculosis? An Analysis of National Prevalence Survey Data from Zambia. *Clinical Infectious Diseases* 2022.
182. ROBINS-E Development Group (Higgins J, Morgan R, Rooney A, Taylor K, Thayer K, Silva R, Lemeris C, Akl A, Arroyave W, Bateson T, Berkman N, Demers P, Forastiere F, Glenn B, Hróbjartsson A, Kirrane E, LaKind J, Luben T, Lunn R, McAleenan A, McGuinness L, Meerpohl J, Mehta S, Nachman R, Obbagy J, O'Connor A, Radke E, Savović J, Schubauer-Berigan M, Schwingl P, Schunemann H, Shea B, Steenland K, Stewart T, Straif K, Tilling K, Verbeek V, Vermeulen R, Viswanathan M, Zahm S, Sterne J). Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E). Launch version, 1 June 2022. Available from: https://www.riskofbias.info/welcome/robins-e-tool.
183. Rubin, D. B. Multiple Imputation for Nonresponse In Surveys (Wiley-Interscience, 2004).
184. Schneider ALC, Pankow JS, Heiss G, Selvin E. Validity and Reliability of Self-reported Diabetes in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2012; **176**(8): 738-43.

185. Yuan X, Liu T, Wu L, Zou Z-Y, Li C. Validity of self-reported diabetes among middle-aged and older Chinese adults: the China Health and Retirement Longitudinal Study. *BMJ open* 2015; **5**(4): e006633.
186. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011. https://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf (accessed 23 January 2023).
187. World Health Organization. National tuberculosis prevalence surveys 2007-2016. Geneva: World Health Organization; 2021. https://apps.who.int/iris/bitstream/handle/10665/341072/9789240022430-eng.pdf accessed 10 January 2023.
188. World Health Organization. Global TB Report 2021. Geneva: World Health Organization; 2021. https://www.who.int/publications/digital/global-tuberculosis-report-2021/featured-topics/tb-diabetes (accessed 23 January 2023).
189. Goldhaber-Fiebert JD, Jeon CY, Cohen T, Murray MB. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. *Int J Epidemiol* 2011; **40**(2): 417-28.
190. Marks SM. Diabetes and tuberculosis, US National Health Interview Survey, 2000–2005 [Short communication]. *The International Journal of Tuberculosis and Lung Disease* 2011; **15**(7): 982-4.
191. Wang Q, Ma A, Han X, et al. Prevalence of Type 2 Diabetes among Newly Detected Pulmonary Tuberculosis Patients in China: A Community Based Cohort Study. *PLoS One* 2013; **8**(12): e82660.
192. Gil-Santana L, Almeida-Junior JL, Oliveira CA, et al. Diabetes Is Associated with Worse Clinical Presentation in Tuberculosis Patients from Brazil: A Retrospective Cohort Study. *PLoS One* 2016; **11**(1): e0146876.
193. van Crevel R, Critchley JA. The Interaction of Diabetes and Tuberculosis: Translating Research to Policy and Practice. *Tropical Medicine and Infectious Disease* 2021; **6**(1): 8.
194. Mishra V, Hong R, Khan S, Gu Y, Liu L. Evaluating HIV estimates from national population-based surveys for bias resulting from non-response. Calverton, Maryland, USA: Macro International, 2008.
195. van't Hoog A, Viney K, Biermann O, Yang B, Leeflang MMG, Langendam MW. Symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative adults and adults with unknown HIV status. *Cochrane Database of Systematic Reviews* 2022; (3).
196. Indian Council of Medical Research (ICMR), National TB Prevalence Survey in India 2019 - 2021. 2021.
197. World Bank. https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html (accessed 23 August 2023).
198. Sutton A, Campbell F. The ScHARR LMIC filter: Adapting a low- and middle-income countries geographic search filter to identify studies on preterm birth prevention and management. *Research Synthesis Methods* 2022; **13**(4): 447-56.
199. National Health, Lung, and Blood institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools Accessed 1 January 2022.

200. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision: updated December 2014 and January 2020. Geneva, Switzerland: WHO, 2020. https://apps.who.int/iris/handle/10665/79199(accessed 4 September 2023).
201. Vincent A, Ian RW, Shahab J, et al. Multiple Imputation for Multilevel Data with Continuous and Binary Variables. *Statistical Science* 2018; **33**(2): 160-83.
202. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; **67**(8): 897-903.
203. Becerra MC, Huang CC, Lecca L, et al. Transmissibility and potential for disease progression of drug resistant Mycobacterium tuberculosis: prospective cohort study. *BMJ* 2019; **367**: l5894.
204. Bekken GK, Ritz C, Selvam S, et al. Identification of subclinical tuberculosis in household contacts using exposure scores and contact investigations. *BMC Infect Dis* 2020; **20**(1): 96.
205. Diaz G, Victoria AM, Meyer AJ, et al. Evaluating the Quality of Tuberculosis Contact Investigation in Cali, Colombia: A Retrospective Cohort Study. *Am J Trop Med Hyg* 2021; **22**: 22.
206. Gr, jean L, Crossa A, et al. Tuberculosis in household contacts of multidrug-resistant tuberculosis patients. *Int J Tuberc Lung Dis* 2011; **15**(9): 1164-9, i.
207. Gr, jean L, Gilman RH, et al. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. *PLoS Medicine / Public Library of Science* 2015; **12**(6): e1001843; discussion e.
208. Marin D, Marin N, Del Corral H, et al. PPD-induced monocyte mitochondrial damage is associated with a protective effect to develop tuberculosis in BCG vaccinated individuals: A cohort study. *PLoS ONE [Electronic Resource]* 2017; **12**(2): e0171930.
209. Shivakumar S, Ch, rasekaran P, et al. Diabetes and pre-diabetes among household contacts of tuberculosis patients in India: is it time to screen them all? *Int J Tuberc Lung Dis* 2018; **22**(6): 686-94.
210. Shu E, Sobieszczyk ME, Sal YRVG, et al. Knowledge of tuberculosis and vaccine trial preparedness in Lima, Peru. *Int J Tuberc Lung Dis* 2017; **21**(12): 1288-93.
211. Verrall AJ, Alisjahbana B, Apriani L, et al. Early Clearance of Mycobacterium tuberculosis: The INFECT Case Contact Cohort Study in Indonesia. *J Infect Dis* 2020; **221**(8): 1351-60.
212. Galea J, Chu AL, Sweetland A, et al. Latent tuberculosis and depressive symptoms in household contacts of persons with active TB: A cohort study. *medRxiv* 2022: 2022.11.15.22282271.
213. Vo LNQ, Nguyen VN, Nguyen NTT, et al. Optimising diagnosis and treatment of tuberculosis infection in community and primary care settings in two urban provinces of Viet Nam: a cohort study. *BMJ open* 2023; **13**(2): e071537.
214. Martinson NA, Lebina L, Webb EL, et al. Household Contact Tracing With Intensified Tuberculosis and Human Immunodeficiency Virus Screening in South Africa: A Cluster-Randomized Trial. *Clin Infect Dis* 2022; **75**(5): 849-56.
215. Allen R, Calderón M, Moore DAJ, Gaskell KM, Curisinche-Rojas M, López S. Feasibility of an mobile application as a tool for multidrug-resistant tuberculosis contact monitoring in Peru. *Rev Peru Med Exp Salud Publica* 2021; **38**(2): 272-7.

216. Guo S, Chongsuvivatwong V, Guo M, et al. Yield, NNS and prevalence of screening for DM and hypertension among pulmonary tuberculosis index cases and contacts through single time screening: A contact tracing-based study. *PLoS One* 2022; **17**(1): e0263308.
217. Kaul S, Nair V, Birla S, et al. Latent Tuberculosis Infection Diagnosis among Household Contacts in a High Tuberculosis-Burden Area: a Comparison between Transcript Signature and Interferon Gamma Release Assay. *Microbiol Spectr* 2022; **10**(2): e0244521.
218. Sharma N, Basu S, Khanna A, Sharma P, Chandra S. The intention to receive tuberculosis preventive therapy in adult household contacts of pulmonary TB patients in Delhi, India. *J Infect Dev Ctries* 2022; **16**(2): 298-304.
219. Smith AGC, Kempker RR, Wassie L, et al. The Impact of Diabetes and Prediabetes on Prevalence of Mycobacterium tuberculosis Infection Among Household Contacts of Active Tuberculosis Cases in Ethiopia. *Open Forum Infectious Diseases* 2022; **9**(7).
220. Narasimhan P, MacIntyre CR, Mathai D, Wood J. High rates of latent TB infection in contacts and the wider community in South India. *Trans R Soc Trop Med Hyg* 2017; **111**(2): 55-61.
221. Zayar NN, Sangthong R, Saw S, Aung ST, Chongsuvivatwong V. Combined Tuberculosis and Diabetes Mellitus Screening and Assessment of Glycaemic Control among Household Contacts of Tuberculosis Patients in Yangon, Myanmar. *Tropical Medicine & Infectious Disease* 2020; **5**(3): 29.
222. Calderon RI, Arriaga MB, Lopez K, et al. High prevalence and heterogeneity of Dysglycemia in patients with tuberculosis from Peru: a prospective cohort study. *BMC Infect Dis* 2019; **19**(1): 799.
223. Kyaw NTT, Sithu A, Satyanarayana S, et al. Outcomes of Community-Based Systematic Screening of Household Contacts of Patients with Multidrug-Resistant Tuberculosis in Myanmar. *Tropical Medicine & Infectious Disease* 2019; **5**(1): 25.
224. Oo MM, Tassanakijpanich N, Phyu MH, et al. Coverage of tuberculosis and diabetes mellitus screening among household contacts of tuberculosis patients: a household-based cross-sectional survey from Southern Thailand. *BMC Public Health* 2020; **20**(1): 957.
225. Kubiak RW, Sarkar S, Horsburgh CR, et al. Interaction of nutritional status and diabetes on active and latent tuberculosis: a cross-sectional analysis. *BMC Infect Dis* 2019; **19**(1): 627.
226. Velen K, Nhung NV, Anh NT, et al. Risk factors for TB among household contacts of patients with smear-positive TB in eight provinces of Vietnam: a nested case-control study. *Clinical Infectious Diseases* 2020; **19**: 19.
227. Abdulkareem FN, Merza MA, Salih AM. First insight into latent tuberculosis infection among household contacts of tuberculosis patients in Duhok, Iraqi Kurdistan: using tuberculin skin test and QuantiFERON-TB Gold Plus test. *Int J Infect Dis* 2020; **96**: 97-104.
228. Lebina L, Fuller N, Osoba T, et al. The Use of Xpert MTB/Rif for Active Case Finding among TB Contacts in North West Province, South Africa. *Tuberculosis Research & Treatment Print* 2016; **2016**: 4282313.
229. Balcells ME, Garcia P, Tiznado C, et al. Association of vitamin D deficiency, season of the year, and latent tuberculosis infection among household contacts. *PLoS ONE [Electronic Resource]* 2017; **12**(4): e0175400.
230. Rajan JV, Ferrazoli L, Waldman EA, et al. Diabetes increases the risk of recent-transmission tuberculosis in household contacts in Sao Paulo, Brazil. *Int J Tuberc Lung Dis* 2017; **21**(8): 916-21.

231. Suggaravetsiri P, Yanai H, Chongsuvivatwong V, Naimpasan O, Akarasewi P. Integrated counseling and screening for tuberculosis and HIV among household contacts of tuberculosis patients in an endemic area of HIV infection: Chiang Rai, Thailand. *Int J Tuberc Lung Dis* 2003; **7**(12): S424-31.
232. Velayutham B, Jayabal L, Watson B, et al. Tuberculosis screening in household contacts of pulmonary tuberculosis patients in an urban setting. *PLoS ONE [Electronic Resource]* 2020; **15**(10): e0240594.
233. Restrepo BI, Camerlin AJ, Rahbar MH, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. *Bull World Health Organ* 2011; **89**(5): 352-9.
234. Polanin JR. Efforts to retrieve individual participant data sets for use in a meta-analysis result in moderate data sharing but many data sets remain missing. *J Clin Epidemiol* 2018; **98**: 157-9.
235. South African Department of Health. National User Guide on the Prevention and Treatment of Hypertension in Adults at the PHC level 2021. https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/HYPERTENSION%2520USER%2520GUIDE%2520FINAL%2520COPY.pdf.
236. amod a, Dave J, mohammed n, Coetzee A. SEMDSA 2017 Guidelines for the Management of Type 2 diabetes mellitus SEMDSA Type 2 Diabetes Guidelines Expert Committee. JEMDSA 2017; 22(1)(Supplement 1): S1-S196; 2019.
237. National Department of Health, South Africa. The National Strategic Plan for the Prevention and Control of Non-Communicable Diseases, 2022 - 2027. Pretoria: National Department of Health, 2022.
238. Community and universal testing for tuberculosis among contacts. https://doi.org/10.1186/ISRCTN10003903.
239. United Republic of Tanzania. The National Tuberculosis and Leprosy Programme. Annual Report 2021. https://ntlp.go.tz/site/assets/files/1157/ntlp_annual_report_2021_final_1.pdf. Accessed 18 January 2023.
240. World Bank, Optima Consortium for Decision Sciences, and Government of South Africa. Optimising Investments in the Tuberculosis Response of Gauteng Province, South Africa. 2019. https://elibrary.worldbank.org/doi/abs/10.1596/33377 Accessed 24 January 2024.
241. National Department of Health, ICF. South Africa Demographic and Health Survey 2016. Pretoria: National Department of Health - NDoH - ICF, 2019.
242. Ministry of Health , Ministry of Health , National Bureau of Statistics , Office of the Chief Government Statistician , ICF. Tanzania demographic and health survey 2022 - final report. Rockville, Maryland, USA: ICF, 2023.
243. Pebesma E. sf: simple features for R. 2018.https://github.com/r-spatial/sf.
244. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* 2021; **385**(19): 1737-49.
245. Levey AS, Eckardt K-U, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67**(6): 2089-100.
246. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *The Lancet Global Health* 2019; **7**(10): e1332-e45.

247. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney International Supplements* 2022; **12**(1): 7-11.
248. Chow, S.-C., Shao, J., Wang, H., & Lokhnygina, Y. (2017). Sample Size Calculations in Clinical Research (3rd ed.). Chapman and Hall/CRC. https://doi.org/10.1201/9781315183084.
249. Venn J. I. On the diagrammatic and mechanical representation of propositions and reasonings. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 1880; **10**(59): 1-18.
250. Yoo JE, Kim D, Han K, Rhee SY, Shin DW, Lee H. Diabetes Status and Association With Risk of Tuberculosis Among Korean Adults. *JAMA Netw Open* 2021; **4**(9): e2126099.
251. Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hypertension and Diabetes Mellitus. *Hypertension* 2018; **71**(3): 422-8.
252. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med* 2012; **13**(8): 453-68.
253. McAlister FA, Straus SE. Evidence based treatment of hypertension. Measurement of blood pressure: an evidence based review. *BMJ* 2001; **322**(7291): 908-11.
254. Arnold M, Beran D, Haghparast-Bidgoli H, et al. Coping with the economic burden of Diabetes, TB and co-prevalence: evidence from Bishkek, Kyrgyzstan. *BMC Health Serv Res* 2016; **16**: 118.
255. Yamanaka T, Castro MC, Ferrer JP, et al. Costs incurred by people with co-morbid tuberculosis and diabetes and their households in the Philippines. *PLoS One* 2024; **19**(1): e0297342.
256. World Health Organization. Saving lives, spending less: the case for investing in noncommunicable diseases. Geneva: World Health Organization; 2021.
257. World Health Organization. 'Best buys' and other recommended interventions for the prevention and control of noncommunicable diseases. Geneva, Switzerland: WHO, 2017.
258. Zayar NN, Chotipanvithayakul R, Htet KKK, Chongsuvivatwong V. Programmatic Cost-Effectiveness of a Second-Time Visit to Detect New Tuberculosis and Diabetes Mellitus in TB Contact Tracing in Myanmar. *Int J Environ Res Public Health* 2022; **19**(23).
259. Sando D, Kintu A, Okello S, et al. Cost-effectiveness analysis of integrating screening and treatment of selected non-communicable diseases into HIV/AIDS treatment in Uganda. *J Int AIDS Soc* 2020; **23**(S1).
260. Basu S, Wagner RG, Sewpaul R, Reddy P, Davies J. Implications of scaling up cardiovascular disease treatment in South Africa: a microsimulation and cost-effectiveness analysis. *The Lancet Global Health* 2019; **7**(2): e270-e80.
261. Department of Health, Republic of South Africa. Symptom-based integrated approach to the adult in primary care. Durban: Department of Health, 2013. https://www.hst.org.za/publications/NonHST%20Publications/PC-101-Guideline-v2-2013-14-2.pdf.
262. Kasaie P, Weir B, Schnure M, et al. Integrated screening and treatment services for HIV, hypertension and diabetes in Kenya: assessing the epidemiological impact and cost-effectiveness from a national and regional perspective. *J Int AIDS Soc* 2020; **23**(S1).
263. Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. *Ann Intern Med* 2010; **152**(8): 481-7, w170-3.

264. Kasaie P, Weir B, Schnure M, et al. Integrated screening and treatment services for HIV, hypertension and diabetes in Kenya: assessing the epidemiological impact and cost-effectiveness from a national and regional perspective. *J Int AIDS Soc* 2020; **23 Suppl 1**(Suppl 1): e25499.
265. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326**(7404): 1427.
266. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2011; **13**(3): 221-8.
267. Wexler DJ. Sulfonylureas and Cardiovascular Safety: The Final Verdict? *JAMA* 2019; **322**(12): 1147-9.
268. Herman ME, O'Keefe JH, Bell DSH, Schwartz SS. Insulin Therapy Increases Cardiovascular Risk in Type 2 Diabetes. *Prog Cardiovasc Dis* 2017; **60**(3): 422-34.
269. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015; **385**(9976): 1397-405.
270. World Health Organization. Tuberculosis patient cost surveys: a handbook. https://apps.who.int/iris/rest/bitstreams/1092601/retrieve accessed 20 December 2021.
271. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-life-tables-by-country.
272. Pillai N, Foster N, Hanifa Y, et al. Patient costs incurred by people living with HIV/AIDS prior to ART initiation in primary healthcare facilities in Gauteng, South Africa. *PLoS One* 2019; **14**(2): e0210622.
273. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998; **18**(2 Suppl): S68-80.
274. Edoka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. *Health Policy Plan* 2020; **35**(5): 546-55.
275. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. *Value Health* 2016; **19**(8): 929-35.
276. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; **139**(25): e1082-e143.
277. Brennan AT, Lauren E, Bor J, et al. Gaps in the type 2 diabetes care cascade: a national perspective using South Africa's National Health Laboratory Service (NHLS) database. *BMC Health Serv Res* 2023; **23**(1): 1452.
278. Bulstra CA, Hontelez JAC, Otto M, et al. Integrating HIV services and other health services: A systematic review and meta-analysis. *PLoS Med* 2021; **18**(11): e1003836.
279. Moonan PK, Zetola NM, Tobias JL, et al. A Neighbor-Based Approach to Identify Tuberculosis Exposure, the Kopanyo Study. *Emerg Infect Dis* 2020; **26**(5): 1010-3.
280. Fatima R, Qadeer E, Yaqoob A, et al. Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection? *PLoS One* 2016; **11**(11): e0165813.

281. Morishita F, Eang MT, Nishikiori N, Yadav RP. Increased Case Notification through Active Case Finding of Tuberculosis among Household and Neighbourhood Contacts in Cambodia. *PLoS One* 2016; **11**(3): e0150405.
282. Sathar F, Velen K, Peterson M, Charalambous S, Chetty-Makkan CM. "Knock Knock": a qualitative study exploring the experience of household contacts on home visits and their attitude towards people living with TB in South Africa. *BMC Public Health* 2020; **20**(1): 1047.
283. Peiris D, Praveen D, Mogulluru K, et al. SMARThealth India: A stepped-wedge, cluster randomised controlled trial of a community health worker managed mobile health intervention for people assessed at high cardiovascular disease risk in rural India. *PLoS One* 2019; **14**(3): e0213708.
284. Schwalm JD, McCready T, Lopez-Jaramillo P, et al. A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial. *Lancet* 2019; **394**(10205): 1231-42.
285. Kumar N, Janmohamed K, Jiang J, et al. Tobacco cessation in low- to middle-income countries: A scoping review of randomized controlled trials. *Addict Behav* 2021; **112**: 106612.
286. Louwagie GM, Okuyemi KS, Ayo-Yusuf OA. Efficacy of brief motivational interviewing on smoking cessation at tuberculosis clinics in Tshwane, South Africa: a randomized controlled trial. *Addiction* 2014; **109**(11): 1942-52.

Appendix 1. Supplementary information for Chapter 5

Search strategy

Medline

1.	exp tuberculosis/
2.	exp Mycobacterium tuberculosis/
3.	tuberculosis.ti,ab,kf.
4.	contact tracing/
5.	contact*.kf,ti,ab.
6.	transmission.kf,ti,ab.
7.	case detection.ti,ab,kf.
8.	screen*.ti,ab,kf.
9.	mass screening/
10.	case finding.ti,ab,kf.
11.	household.kf,ti,ab.
12.	family.kf,ti,ab.
13.	household/
14.	house.kf,ti,ab.
15.	home.ti,ab,kf.
16.	family characteristics/
17.	or/1-3
18.	or/3-9
19.	or/10-15
20.	16 and 17 and 18
21.	limit 19 to yr="2000 -Current"

22.	(afghanistan or albania or algeria or american samoa or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrain or bangladesh or barbados or republic of belarus or belarus or byelarus or belorussia or byelorussian or belize or british honduras or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or burkina faso or burkina fasso or upper volta or burundi or urundi or cabo verde or cape verde or cambodia or kampuchea or khmer republic or cameroon or cameron or cameroun or central african republic or ubangi shari or chad or chile or china or colombia or comoros or comoro islands or iles comores or mayotte or democratic republic of the congo or democratic republic congo or congo or zaire or costa rica or "cote d'ivoire" or "cote d' ivoire" or cote divoire or cote d ivoire or ivory coast or croatia or cuba or cyprus or czech republic or czechoslovakia or djibouti or french somaliland or dominica or dominican republic or ecuador or egypt or united arab republic or el salvador or equatorial guinea or spanish guinea or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or gabonese republic or gambia or "georgia (republic)" or georgian or ghana or gold coast or gibraltar or greece or grenada or guam or guatemala or guinea or guinea bissau or guyana or british guiana or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or isle of man or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people's republic of korea" or republic of korea or north korea or south korea or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or kyrgyz republic or kirghiz or laos or lao pdr or "lao people's democratic republic" or latvia or lebanon or lebanese republic or lesotho or basutoland or liberia or libya or libyan arab jamahiriya or lithuania or macau or macao or republic of north macedonia or macedonia or madagascar or malagasy republic or malawi or nyasaland or malaysia or malay federation or malaya federation or maldives or indian ocean islands or indian ocean or mali or malta or micronesia or federated states of micronesia or kiribati or marshall islands or nauru or northern mariana islands or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or morocco or ifni or mozambique or portuguese east africa or myanmar or burma or namibia or nepal or netherlands antilles or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or papua new guinea or new guinea or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's republic" or portugal or portuguese republic or puerto rico or romania or russia or russian federation or ussr or soviet union or union of soviet socialist republics or rwanda or ruanda or samoa or pacific islands or polynesia or samoan islands or navigator island or navigator islands or "sao tome and principe" or saudi arabia or senegal or serbia or seychelles or sierra leone or slovakia or slovak republic or slovenia or melanesia or solomon island or solomon islands or norfolk island or norfolk islands or somalia or south africa or south sudan or sri lanka or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or saint lucia or "st. lucia" or "saint vincent and the grenadines" or saint vincent or "st. vincent" or grenadines or sudan or suriname or surinam or dutch guiana or netherlands guiana or syria or syrian arab republic or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or timor leste or east timor or togo or togolese republic or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu

	or new hebrides or venezuela or vietnam or viet nam or middle east or west bank or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or northern rhodesia or global south or africa south of the sahara or sub-saharan africa or subsaharan africa or africa, central or central africa or africa, northern or north africa or northern africa or magreb or maghrib or sahara or africa, southern or southern africa or africa, eastern or east africa or eastern africa or africa, western or west africa or western africa or west indies or indian ocean islands or caribbean or central america or latin america or "south and central america" or south america or asia, central or central asia or asia, northern or north asia or northern asia or asia, southeastern or southeastern asia or south eastern asia or southeast asia or south east asia or asia, western or western asia or europe, eastern or east europe or eastern europe or developing country or developing countries or developing nation? or developing population? or developing world or less developed countr* or less developed nation? or less developed population? or less developed world or lesser developed countr* or lesser developed nation? or lesser developed population? or lesser developed world or under developed countr* or under developed nation? or under developed population? or under developed world or underdeveloped countr* or underdeveloped nation? or underdeveloped population? or underdeveloped world or middle income countr* or middle income nation? or middle income population? or low income countr* or low income nation? or low income population? or lower income countr* or lower income nation? or lower income population? or underserved countr* or underserved nation? or underserved population? or underserved world or under served countr* or under served nation? or under served population? or under served world or deprived countr* or deprived nation? or deprived population? or deprived world or poor countr* or poor nation? or poor population? or poor world or poorer countr* or poorer nation? or poorer population? or poorer world or developing econom* or less developed econom* or lesser developed econom* or under developed econom* or underdeveloped econom* or middle income econom* or low income econom* or lower income econom* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmics or third world or lami countr* or transitional countr* or emerging economies or emerging nation?).ti,ab,sh,kf.
23.	20 and 21

EMBASE

1	tuberculosis/
2	tuberculosis.ti,ab,kw.
3	contact$.de.
4	contact tracing.kw,ti,ab.
5	transmission.ti,ab,kw.
6	case detection.ti,ab,kw.
7	contact.kw,ti,ab.
8	screen*.ti,ab,kw.
9	case finding.ti,ab,kw.
10	screening/
11	household.kw,ti,ab.
12	family.kw,ti,ab.
13	household/
14	house.kw,ti,ab.
15	home.ti,ab,kw.
16	1 or 2
17	or/3-10
18	or/11-15
19	and/16-18
20	limit 19 to yr="2000 - 2021"
21	(afghanistan or albania or algeria or american samoa or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrain or bangladesh or barbados or republic of belarus or belarus or byelarus or belorussia or byelorussian or belize or british honduras or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or burkina faso or burkina fasso or upper volta or burundi or urundi or cabo verde or cape verde or cambodia or kampuchea or khmer republic or cameroon or cameron or cameroun or central african republic or ubangi shari or chad or chile or china or colombia or comoros or comoro islands or iles comores or mayotte or democratic republic of the congo or democratic republic congo or congo or zaire or costa rica or "cote d'ivoire" or "cote d' ivoire" or cote divoire or cote d ivoire or ivory coast or croatia or cuba or cyprus or czech republic or czechoslovakia or djibouti or french somaliland or dominica or dominican republic or ecuador or egypt or united arab republic or el salvador or equatorial guinea or spanish guinea or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or gabonese republic or gambia or "georgia (republic)" or georgian or ghana or gold coast or gibraltar or greece or grenada or guam or guatemala or guinea or guinea bissau or guyana or british guiana or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or isle of man or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people's republic of korea" or republic of korea or north korea or south korea or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or kyrgyz republic or kirghiz or laos or lao pdr or "lao people's democratic republic" or latvia or lebanon or lebanese republic or lesotho or basutoland or liberia or libya or libyan arab jamahiriya or lithuania or macau or macao or republic of north macedonia or macedonia or madagascar or malagasy republic or malawi or nyasaland or malaysia or malay federation or malaya federation or maldives or indian ocean islands or indian ocean or mali or malta or

	micronesia or federated states of micronesia or kiribati or marshall islands or nauru or northern mariana islands or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or "montenegro (republic)" or morocco or ifni or mozambique or portuguese east africa or myanmar or burma or namibia or nepal or netherlands antilles or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or papua new guinea or new guinea or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's republic" or portugal or portuguese republic or puerto rico or romania or russia or russian federation or ussr or soviet union or union of soviet socialist republics or rwanda or ruanda or samoa or pacific islands or polynesia or samoan islands or navigator island or navigator islands or "sao tome and principe" or saudi arabia or senegal or serbia or seychelles or sierra leone or slovakia or slovak republic or slovenia or melanesia or solomon island or solomon islands or norfolk island or norfolk islands or somalia or south africa or south sudan or sri lanka or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or saint lucia or "st. lucia" or "saint vincent and the grenadines" or saint vincent or "st. vincent" or grenadines or sudan or suriname or surinam or dutch guiana or netherlands guiana or syria or syrian arab republic or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or timor leste or east timor or togo or togolese republic or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or "turkey (republic)" or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu or new hebrides or venezuela or vietnam or viet nam or middle east or west bank or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or northern rhodesia or global south or africa south of the sahara or "sub saharan africa" or subsaharan africa or africa, central or central africa or africa, northern or north africa or northern africa or magreb or maghrib or sahara or africa, southern or southern africa or africa, eastern or east africa or eastern africa or africa, western or west africa or western africa or west indies or indian ocean islands or caribbean region or caribbean islands or caribbean or central america or latin america or "south and central america" or south america or asia, central or central asia or asia, northern or north asia or northern asia or asia, southeastern or southeastern asia or south eastern asia or southeast asia or south east asia or asia, western or western asia or europe, eastern or east europe or eastern europe or developing country or developing countries or developing nation? or developing population? or developing world or less developed countr* or less developed nation? or less developed population? or less developed world or lesser developed countr* or lesser developed nation? or lesser developed population? or lesser developed world or under developed countr* or under developed nation? or under developed population? or under developed world or underdeveloped countr* or underdeveloped nation? or underdeveloped population? or underdeveloped world or middle income countr* or middle income nation? or middle income population? or low income countr* or low income nation? or low income population? or lower income countr* or lower income nation? or lower income population? or underserved countr* or underserved nation? or underserved population? or underserved world or under served countr* or under served nation? or under served population? or under served world or deprived countr* or deprived nation? or deprived population? or deprived world or poor countr* or poor nation? or poor population? or poor world or poorer countr* or poorer nation? or poorer population? or poorer world or developing econom* or less developed econom* or lesser developed econom* or under developed econom* or underdeveloped econom* or middle income econom* or low income econom* or lower income econom* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmics or third world or lami countr* or transitional countr* or emerging economies or emerging nation?).ti,ab,sh,kw.
22	19 and 21

Global index medicus
tuberculosis AND (household OR family OR home) AND contact

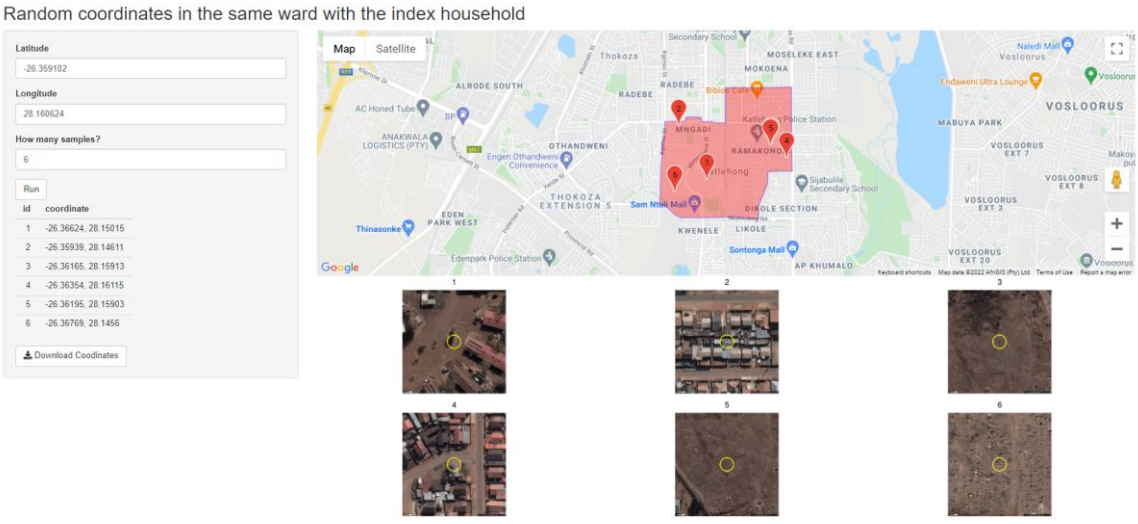
Appendix 2. Supplementary information for Chapter 6

Method and procedure for the recruitment of neighbourhood households in South Africa

Geo-coordinates of index households were collected using Redcap. These coordinates were used to identify households within the same ward as the TB patients using the R package 'sf' (https://cran.r-project.org/web/packages/sf/index.html). I developed an interactive web application to generate random coordinates in the same ward as an index household using the Shiny package available on R (https://shiny.posit.co/).

Figure 1 shows the interface of the interactive web application. By entering the coordinates of an index household, the application generates up to six random coordinates within the same ward. The randomly selected locations are overlaid on a Google satellite image.

Figure 1. Web application to generate random coordinates in the same ward with an index household



Once the coordinates were identified, I used Google satellite images to select coordinates corresponding to houses and created a list of households for invitation. The coordinates of these households were shared with my field team as a Google Map link, allowing the team to easily navigate to the location with a simple click of the link.

The team invited the first household on the list. If the first household declined, they invited the next one on the list, continuing this process until one neighbourhood household was enrolled.

Lesson learnt

This method worked very well without issues in Ekurhuleni and the city of Mbeya, allowing the identification of control households randomly. However, there were challenges in rural areas of the Mbeya region.

First, Google satellite images are updated less frequently in less populated areas (https://www.gearthblog.com/blog/archives/2016/07/how-often-is-google-earth-imagery-updated-the-continental-us.html). In fact, during the pilot of this recruitment approach, I identified inconsistencies with the satellite images. Second, in some rural areas, there were only a few households available in a neighbourhood. As a result, the randomly generated coordinates rarely corresponded to households, necessitating the repeated generation of random coordinates.

Third, the internet connection was poor, making it challenging to identify new coordinates on-site when the households on the list were exhausted. Fourth, there were areas not accessible by car, so the team had to walk to visit households. This was particularly challenging when a distant coordinate was identified by chance, and the team had to walk to the next location if the first coordinate failed to identify a household or if the household declined to participate.

Because of these challenges, in rural areas of the Mbeya region, I decided to invite the closest available household.

Appendix 3. Supplementary information for chapter 7

Questionnaire: The initial cost of care for non-communicable diseases in household contacts who are newly diagnosed with non-communicable disease (NCD).

Question	
1. Have you been hospitalized because of NCD since referral? If yes, go to another questionnaire for individuals who were hospitalized	Yes/No
2. How many clinic visits related to NCD have you had so far since referral (to see the doctor or nurse, have follow- up tests, etc.)?	_____Times
Costs required for out-patient visits (repeat 2.1-2.10 for each visit indicated above).	
2.1 Which of the following types of facilities did you seek care?	**1. Public clinic/hospital** **2. Private clinic/hospital** **3. General practitioner (GP)** **4. Traditional Healer** **5. Pharmacy** **6. Other (specify)**
How long did this clinic visit take, including travel time and waiting time (total turnaround time)?	**Travel time (round trip)**
	Time at clinic
2.2 What was the cost of transport (round trip) at the last follow-up medical outpatient visit, including parking, in total for you and any accompanying household member?	
2.3 Did you require accommodation for this visit for staying near the clinic?	Yes/No
If yes, what accommodation cost did you have for this visit, in total, for you and any accompanying household member?	
2.4 Did you have to pay for food as a result of travelling to the hospital/clinic?	Yes/No
If yes, how much did the food cost for this visit, in total, for you and any accompanying household member?	
2.5 What fees did you pay during this medical outpatient visit for registration/consultation?	
2.6 Did you undergo radiography and other imaging?	Yes/ No
If yes, what imaging did you undergo?	Name of the imaging:

What did you pay for this in total?	
2.7 Did you undergo any tests for NCD and others during this medical outpatient visit? They include blood pressure measurement, urine tests, blood tests, peak flow meter, Electrocardiograph and others.	Yes/No
If yes, what did you undergo?	Name of the test:
What did you pay for this in total?	
2.8 Did you require other procedures?	Yes/No
If yes, what were they?	
What fees did you pay for this?	
2.9 Did you lose income because of this visit, for example, because you had to leave from your work?	Yes/No
If yes, how much?	
2.10 Did anyone accompany you to the clinic?	Yes/No
If yes, did that person lose an income during that time?	
2.11 What is his/her monthly income?	
2.12 If you don't want to tell the exact amont, can you tell the category his/her monthly income belong to?	**1 = < R 600** **2 = R 601-1000** **3 = R 1001-2000** **4 = R 2001-4000** **5 = > R 4000** **99 = Don't know** **97 Refused to Answer**
2.13 Did you have to pay for anything else because of this visit (e.g. child care)?	Yes/No
If yes, what were they?	
What fees did you pay for this?	
2.14 Did you get reimbursement for this visit from insurance?	Yes/No
If yes, how much was reimbursed	
Cost for food	
3.1 Did you have to change your diet because of NCD, for example, to eat more vegetables and fruits, as recommended by health care staff?	Yes/No
If yes, how much did you spend on this additional food in the past week approximately?	

Equipment		
4. Did you have to buy any special equipment because of your NCD diagnosis (e.g. glucose meter and blood pressure monitor)	Yes/No	
If yes, what equipment did you buy?	Blood pressure monitor	Cost: Name: Maker:
	Blood glucose monitor	Name: Maker: Cost:
	Other	Name: Maker: Cost:

Medication				
5.1 List any medications that you were given to treat non-communicable diseases They include medicines to lower blood pressure, blood sugar, or cholesterol.	**Name**	**Dosage (if known)**	**Frequency per day**	**Duration (in days)**
5.2 What fees did you pay for <u>medicines treating NCD</u>, including prescriptions for medicines bought outside the facility?	**None or specific the amount**			
5.3 Were they reimbursed by insurance?	**Yes/No**			
If yes, how much were reimbursed?				
5.4 List any other medicines you were given.	**Name**	**Dosage (if known)**	**Frequency per day**	**Duration (in days)**

5.5 What fees did you pay for other <u>medicines</u>, including prescriptions for medicines bought outside the facility?				
5.6 Were they reimbursed by insurance?	**Yes/No**			
If yes, how much was reimbursed?				
5.7 Were you prescribed insulin?	**Yes/No**			
If yes,	**Dose**	**Frequency**	**Expense**	
Were they reimbursed by insurance?	**Yes/No**			
If yes, how much was reimbursed?				
Your income				
What is your individual monthly income?				
If you don't want to tell the exact amont, can you tell the category your monthly income belong to?	**1 = < R 600** **2 = R 601-1000** **3 = R 1001-2000** **4 = R 2001-4000** **5 = > R 4000** **99 = Don't know** **97 Refused to Answer**			

Questionnaire for individuals who were hospitalized because of NCD.

1. How many times were you hospitalized?	_____Times
Costs required for hospitalization (repeat 2.1-2.10 for each visit indicated above).	
2.1 Which of the following types of facilities were you hospitalized?	**1. Public hospital** **2. Private hospital**
2.2 Number of days hospitalized	**days**

2.3 Did you have to pay for food during hospitalization?	Yes/No
If yes, how much did the food cost for this hospitalization, in total, for you and any accompanying household member?	
2.4 What fees did you pay during this medical outpatient visit for registration/consultation?	
2.5 Did you undergo radiography and other imaging (e.g. ultrasonography) ?	Yes/ No
If yes, what imaging did you undergo?	Name of the imaging:
What did you pay for this in total?	
2.6 Did you undergo any tests for NCD and others during this hospitalization? They include blood pressure measurement, urine tests, blood tests, peak flow meter, Electrocardiograph and others.	Yes/No
If yes, what did you undergo?	Name of the test:
What did you pay for this in total?	
2.7 Did you require other procedures (e.g. biopsy and surgery)?	Yes/No
If yes, what were they?	
What fees did you pay for this?	
2.8 Were you given any medications during the hospitalization?	Yes/No
What did you pay for this in total?	
2.9 Did anyone accompany you during the hospitalization?	Yes/No
If yes, did that person lose an income during that time?	
What is his/her individual monthly income?	**1 = < R 600**
If you don't want to tell the exact amont, can you tell the category his/her monthly income belong to?	**1 = < R 600** **2 = R 601-1000** **3 = R 1001-2000** **4 = R 2001-4000** **5 = > R 4000** **99 = Don't know** **97 Refused to Answer**
2.10 Did you have to pay for anything else because of this hospitalization (e.g. payment for linen, soap, other services & administrative)?	Yes/No
If yes, what were they?	
What fees did you pay for this?	

2.11 Did you have to pay day charges (e.g. consultation fee) during the hospitalization in addition to costs for the above items?	Yes/No
If yes, how much was it per day?	Per day
2.12 Did you get reimbursement for this visit from insurance?	Yes/No
If yes, how much was reimbursed	