**Title:** Tuberculosis incidence and body mass index – an updated systematic literature review and global analysis.

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## RESEARCH IN CONTEXT

### Evidence before this study

We did a preliminary scoping search in Medline in February 2024 to identify review articles exploring the association between nutritional status and tuberculosis incidence, using medical subject headings and title and abstract search terms including “tuberculosis”; “body mass index”; and “undernutrition”.

Ecological evidence shows that large reductions in tuberculosis burden occurred in Europe and North America during the early 20$^{th}$ century, which are widely attributed to socioeconomic development and consequent improved nutrition and living conditions. More recent modelling and interventional studies support this and suggest important reductions in tuberculosis incidence could be achieved by improving population nutritional status. A systematic review from 2009 demonstrated an inverse log-linear association between tuberculosis incidence and body mass index (BMI) – a measure of weight relative to height commonly used to classify nutritional status, including undernutrition when people are underweight (BMI<18.5kg/m$^2$). For each additional one unit increase in BMI, tuberculosis incidence declined by 13.8% across included studies. However, the review was limited to six studies in high-income countries mostly in selected populations with a low HIV prevalence, and was only able to demonstrate this association in the normal to overweight BMI range (18.5-30.0kg/m$^2$). A 2024 Cochrane review added studies from low- and middle-income countries but did not further examine the log-linear association between tuberculosis incidence and BMI and has methodological limitations.

### Added value of this study

Our review adds evidence from 36 new studies describing 39 cohorts across high through low-income countries and BMI values ranging from 15kg/m$^2$ through to 35kg/m$^2$. The additional data also allowed us to extend the analysis beyond general population cohorts, enabling analyses of the association between tuberculosis incidence and BMI for people living with HIV and people with diabetes.

### Implications of all the evidence

Taken together, the empirical evidence demonstrates the fundamental independent importance of nutritional status as a determinant of tuberculosis, highlighting the need for social protection and other interventions to improve nutrition as part of a holistic global tuberculosis response. Nevertheless, additional evidence from low- and middle-income countries remains valuable, and further research is needed to more comprehensively understand the pathways through which nutritional status influences tuberculosis risk.

## ABSTRACT

**Background.** Undernutrition is the leading population-level determinant of tuberculosis, but the relationship between tuberculosis and nutritional status remains poorly understood. We refined and extended a 2009 review to establish the association between tuberculosis incidence and the full body mass index (BMI) range in key populations across high-income (HIC) and low and middle-income countries (LMIC).

**Methods.** We systematically searched Medline and Embase for new studies published between 2009 and 2024 investigating tuberculosis incidence and nutritional status in adults and extracted estimates of incidence and BMI distributions. To capture uncertainty, we randomly drew 1,000 datasets from these distributions. For each dataset, we fitted a log-linear model across included studies and calculated the mean reduction in tuberculosis incidence per one unit increase in BMI, with 95% uncertainty intervals (95%UI). Using random effects meta-analyses, we estimated the incidence rate ratio (IRR) and 95% confidence interval (95%CI) for underweight (BMI<18.5kg/m$^2$) versus not underweight (BMI≥18.5kg/m$^2$). We stratified results by population group and country income status where possible.

**Findings.** We screened 8,881 abstracts, reviewed 127 full-text articles, and included 42 studies describing 45 cohorts – 39 from our search and six from the 2009 review. We observed a consistent inverse log-linear association between tuberculosis incidence and BMI in the underweight to obese BMI range (15.0-35.0kg/m$^2$). Using unadjusted rates, the mean reduction in tuberculosis incidence per unit increase in BMI was 12.3% (95%UI: 10.8-13.8) in 19 general population cohorts (n=24,917,920); 9.7% (95%UI: 7.3-12.3) in eight cohorts of people with HIV (n=134,031); and 16.1% (95%UI: 12.3-19.2) in two cohorts of people with diabetes (n=1,117,991). In the meta-analyses, the IRR for tuberculosis comparing underweight versus not underweight was 3.05 (95%CI: 2.46-3.77) in 17 general population cohorts (n=22,282,841); 2.80 (95%CI: 2.45-3.21) in 18 cohorts of people with HIV (n=160,222); and 4.11 (95%CI: 3.74-4.51) in three cohorts of people with diabetes (n=1,118,424). Results were consistent when using estimates adjusted for confounding.

**Interpretation.** We demonstrated an inverse log-linear association between tuberculosis incidence and BMI across a wide range of nutritional status and populations, including LMIC, people with HIV and people with diabetes. Our findings demonstrate the importance of ensuring interventions to improve nutrition become an integral component of the global tuberculosis response.



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## INTRODUCTION

The global tuberculosis epidemic remains a leading cause of ill health and socioeconomic consequences among individuals, their households, and communities.[1] In 2022, tuberculosis affected an estimated 10.6 million people and killed 1.3 million, over 80% of whom were living in low- and middle-income countries (LMIC).[2] Although incidence and mortality have declined since 2010, the pace of decline is inadequate to achieve World Health Organization (WHO) End TB Strategy 2025 targets and has been partially reversed by the impact of COVID-19.[2,3] One potential reason for this is the lack of action to address social determinants such as undernutrition, which have been demonstrated in several studies to be key drivers of tuberculosis incidence.[4-6]

Both the WHO End TB Strategy and the United Nations (UN) Sustainable Development Goals (SDG) now conceptualise tuberculosis as a development challenge and explicitly call for poverty reduction interventions and action on underlying social determinants, in addition to equitable expansion of new and existing biomedical interventions.[3,7] Undernutrition is the leading driver of tuberculosis, responsible for an estimated 21% (2.2 million) of tuberculosis cases in 2022, higher than HIV, alcohol use disorders, smoking, and diabetes.[2,8,9] In countries with a high prevalence of undernutrition, including many with a high HIV prevalence, the population attributable fraction (PAF) of tuberculosis due to undernutrition is considerably higher.[2,10]

Although undernutrition is generally considered as a binary concept for calculating a PAF, this is a simplification of a complex relationship between tuberculosis and nutritional status. A 2009 review of six prospective studies demonstrated an inverse log-linear association between tuberculosis incidence and body mass index (BMI, expressed as $kg/m^2$), a widely used indicator of nutritional status, in the normal to overweight BMI range (18.5-30.0$kg/m^2$).[11] This was limited to high-income countries (HIC) and only crudely illustrated uncertainty in tuberculosis incidence, but not BMI. A more recent Cochrane review included studies from a wider range of populations, but did not further investigate the log-linear association demonstrated previously, pooled together effect estimates of undernutrition with different definitions and reference groups, excluded important historical and more recent studies, and was limited to only using estimates adjusted for confounders.[12]

In this study we aimed to address these limitations and comprehensively characterise the association between tuberculosis incidence and nutritional status in adults.

## METHODS

### Search strategy and selection criteria

We systematically reviewed the literature for studies investigating the association between tuberculosis incidence and nutritional status. As the 2009 review[11] covered literature published until December 2008, we searched Medline and Embase for additional studies published between 1st January 2009 and 28th March 2024. The search terms used were developed in consultation with a librarian (**Appendix, page 1**). In addition, we screened the references of included articles; two related reviews;[13,14] the recent Cochrane review;[12] and sought expert opinion on potential studies from our collaborators.

We included prospective and retrospective cohort studies that reported height and weight or BMI at baseline, and which had tuberculosis as the outcome. We applied no restrictions on publication status or language. We excluded case-control studies (unless nested within a cohort); studies with self-reported tuberculosis, tuberculosis mortality, or *Mycobacterium tuberculosis* infection as the outcome; studies that were only done in people aged<18 years because of differences in anthropometric measures and tuberculosis diagnosis; studies done in specific populations with limited generalisability (e.g. people who had a recent gastrectomy); and conference abstracts which were later published as full articles, or those with insufficient data. The primary aim was to explore the association between tuberculosis incidence and BMI. For this, we only included studies that provided estimates of incidence in at least three BMI categories. The secondary aim was to estimate the risk of incident tuberculosis in adults who are underweight (defined as BMI<18.5kg/m$^2$). For this, we only included studies that reported a direct comparison of underweight versus not underweight (BMI≥18.5kg/m$^2$); or studies from which the available or shared data could be used to directly calculate this estimate.

Two authors (MJS and JPC) reviewed the full texts of studies included in the 2009 review[11], as well as those returned by the updated search after removing duplicates and screening titles and abstracts. Where studies were considered potentially eligible, but the available data were not suitable in their published form, we contacted authors for clarifications and/or to request additional data. Specifically, we requested estimates of tuberculosis incidence in different BMI categories reported as the number of events/number of person-years follow-up or per 100,000 person-years; the mean, standard deviation (SD), and range for BMI in the study population; and unadjusted and adjusted estimates of the hazard ratio (HR) or incidence rate ratio (IRR) for underweight versus not underweight. Where there were doubts about whether a study should be included, these were resolved in discussion with a third author (CFQ). We checked for overlap of study populations between articles to avoid double-counting. Where there was overlap, we included the article which either already reported data in the correct format; had a primary aim of exploring the association between tuberculosis and nutritional status; or had the longest follow-up.

### Data analysis

Data were extracted from published manuscripts and supplementary appendices/data files into a data extraction form by MJS and JPC. We classified studies by population (general population, people with HIV, and people with diabetes) and whether they were conducted in HIC or LMIC; and stratified our analyses by population and country income group where possible. For all studies, we extracted data on the number and

type of study participants, the years of recruitment, the mean duration of follow-up per participant, how tuberculosis was defined and ascertained; and which variables were controlled for in adjusted analyses. We did not quantitatively assess the risk of bias or clinical/methodological heterogeneity in included studies. Analyses were performed using Stata (version 18, StataCorp) and RStudio (version 2023.03.1+446) and all p values generated were two-sided.

To explore the association between tuberculosis incidence and BMI, we extracted unadjusted estimates of tuberculosis incidence rates for the BMI categories reported in each study (e.g. 18.5-25.0kg/$m^2$), with their 95% confidence intervals (95%CI). If 95%CI were not reported, we calculated them based on the reported number of events and number of person-years follow-up. All incidence rates were transformed into rates per 100,000 person-years. We also extracted the mean, SD, and BMI range for the study population. To capture uncertainty in both tuberculosis incidence and BMI, we randomly drew 1,000 datasets of tuberculosis incidence and BMI values for each reported BMI category, assuming they were both log-normally distributed. When key BMI data were missing, we used an optimisation function to estimate mean and SD; and data from other studies to provide an approximate range (**Appendix, pages 2-6**). Then, for each analysis group (e.g. studies done in the general population in LMIC), we fitted a log-linear model to each of the 1,000 simulated datasets, combining data across included studies in that analysis group with equal weighting. From these 1,000 models, we calculated the mean reduction in tuberculosis incidence per unit increase in BMI, with 95% uncertainty intervals (95%UI). We then created visualisations for each individual study. We plotted the mean and 95%UI for the 1,000 resampled incidence values in each BMI category, along with the median and interquartile range for the 1,000 resampled BMI values in each BMI category. Finally, we overlaid the mean log-linear reduction line (with 95%UI) calculated from the combined analysis onto these individual study plots.

To estimate the risk of incident tuberculosis in adults who are underweight, we extracted unadjusted estimates of the IRR or HR reported by each study comparing participants who were underweight (BMI<18.5kg/$m^2$) versus those not underweight (BMI≥18.5kg/$m^2$), with their 95%CI. Where these estimates were not reported, we calculated an IRR/HR with 95%CI using the available data. For the purposes of pooling estimates in meta-analysis, we considered the IRR and HR to be approximately equivalent.[15] We calculated the natural logarithms of the extracted IRR and 95%CI and then estimated the standard error (SE) using the formula: SE=(log(upper 95%CI) – log(lower 95%CI))/3.92. We used random effects meta-analyses to estimate the overall IRR, based on the assumption that the true effect might vary across studies due to differences in design or populations. We used the Restricted Maximum Likelihood Method (REML) to estimate the between-study variance ($\tau^2$), and the $I^2$ statistic to assess heterogeneity. Alongside the 95%CI for the overall estimate, we also calculated the 95% prediction interval.

**Sensitivity analyses**

We repeated these analyses using estimates adjusted for the confounders in each study**.** To calculate adjusted incidence rates in different BMI categories, we multiplied the crude incidence rate in the reference BMI category by the point estimate and 95%CI for the adjusted HR or IRR reported for each BMI category.

**Role of the funding source**

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## RESULTS

After removing duplicates, our search yielded 8,881 records, of which 127 articles were sought for full-text review. 42 studies describing 45 cohorts were eligible for inclusion – 36 (39 cohorts) were identified in our new search, and six were from the previous review (**Figure 1**). All included studies were cohort studies (some embedded in randomised trials), with recruitment undertaken between 1949 and 2019. An overview of study characteristics is shown in **Table 1.**

The total sample size was 26,208,583. There were 14 cohorts in the WHO Western Pacific Region (n=23,367,091; 89% of the total population), dominated by two large studies in South Korea;[16-27] two in the European Region (n=1,744,630; 6.7%);[28,29] seven in the Region of the Americas (n=929,140; 3.6%);[30-36] 18 in the African Region (n=143,671; 0.55%);[37-53] and four in the South-East Asian region (n=24,051; 0.09%).[54-57] No eligible cohorts were identified from the Eastern Mediterranean Region. 23 cohorts were eligible to be included in both the BMI and underweight analyses;[16-19,21-27,30-32,35,36,40,45,46,55,57] 16 were only included in the underweight analyses;[20,37-39,41,42,44,47-50,52-54,56] and six were only included in the BMI analyses.[28,29,33,34,43,51] There were important differences in populations, which ranged from general population-based cohorts among healthy individuals (mostly in the Western Pacific Region),[16-19,21-23,25-29,32-34] to specific cohorts of people with HIV (mostly in the African Region).[20,31,37-41,43-53,55,57] There were also five cohorts of household contacts of people with tuberculosis (three in Peru and two in India),[30,35,36,54,56] which we grouped with general population cohorts, and three cohorts of people with diabetes.[19,24,42] Most cohorts used a broad definition of all forms of tuberculosis as the outcome, which included both pulmonary and extra-pulmonary tuberculosis diagnosed either microbiologically or clinically and radiologically. Tuberculosis was mostly diagnosed as per local protocols and practices and ascertained by researchers using clinic registers and by linking identification data to national tuberculosis surveillance and mortality systems. Some studies undertook active follow-up including home visit interviews and tuberculosis testing. The mean follow-up time per participant in each cohort ranged from 0.83 to 16.9 years, with a mean across all 45 cohorts of 4.1 years.

Tuberculosis incidence rates in different categories of BMI for each study are shown in the **Appendix** (**pages 4-6**). We observed a consistent inverse log-linear association between tuberculosis incidence and BMI in the underweight to obese BMI range (15.0-35.0kg/m$^2$). In the analysis using unadjusted incidence rates, across 19 general population cohorts, 13 in HIC and six in LMIC, the mean reduction in tuberculosis incidence per one unit increase in BMI was 12.3% (95%UI: 10.8-13.8) (**Figure 2**). This was similar in cohorts from HIC and LMIC (**Appendix, pages 7-8**). Across eight cohorts of people with HIV, all of which were in LMIC, the mean reduction was 9.7% (95%UI: 7.3-12.3) (**Figure 3a**); and across two cohorts of people with diabetes, one in a HIC and one in an LMIC, the mean reduction was 16.1% (95%UI: 12.3-19.2) (**Figure 3b**). These unadjusted results equate to an estimated relative risk of tuberculosis for a BMI of 16.0kg/m$^2$ versus 25.0kg/m$^2$ of 2.84 (95%UI: 2.52-3.20) in the general population; 2.30 (1.89-2.84) among people with HIV; and 3.83 (95%UI: 2.84-4.86) among people with diabetes. In the sensitivity analyses using incidence rates adjusted for the confounders originally controlled for in each study (**Table 1**), these results did not change significantly (**Appendix, pages 9-13**). The adjusted results equate to an estimated adjusted relative risk of tuberculosis for a BMI of 16.0kg/m$^2$ versus 25.0kg/m$^2$ of 2.84 (95%UI: 2.48-3.23) in the general population; 2.54 (95%UI: 1.92-3.57) among people with HIV; and 2.96 (95%UI: 2.24-3.69) among people with diabetes.

IRR for tuberculosis comparing underweight versus not underweight for each study are shown in the **Appendix (pages 14-15)**. In the meta-analysis using unadjusted IRR, in 17 general population cohorts the pooled IRR was 3.05 (95%CI: 2.46-3.77) (**Figure 4**). This was similar in cohorts from HIC and LMIC (**Appendix, page 16**). In 18 cohorts of people with HIV, the pooled IRR was 2.80 (95%CI: 2.45-3.21) (**Figure 5a**); and in three cohorts of people with diabetes, the pooled IRR was 4.11 (95%CI: 3.74-4.51) (**Figure 5b**). There was significant heterogeneity in most meta-analyses. In the sensitivity analyses using adjusted IRR, these results were similar (**Appendix, page 17**), although the number of included cohorts was smaller and there were not sufficient studies to conduct a meta-analysis of adjusted IRR for people with diabetes or for general population cohorts disaggregated by country income.

## DISCUSSION

In this updated systematic literature review and analysis, we refined and extended findings of the 2009 review[11] demonstrating a consistent inverse log-linear association between tuberculosis incidence and BMI. Through inclusion of over six times the number of cohorts and comprehensively accounting for uncertainty in both incidence and BMI, we confirmed the log-linear association across the full underweight to obese BMI range (15.0-35.0kg/m$^2$); now include cohorts from a range of HIC and LMIC; and demonstrated the association in not just general population cohorts (mostly undertaken in areas with low HIV prevalence) but also in people with HIV, and people with diabetes.

The strength of the log-linear association and the homogeneity across populations with varying background rates of tuberculosis incidence, even after adjusting for a range of potential confounders, is striking and highlights the fundamental independent importance of nutritional status in tuberculosis epidemiology. This has been most recently demonstrated in the RATIONS trial, which showed that providing nutritional support to household contacts of people with tuberculosis reduced the risk of incident tuberculosis by approximately 40%.[58] Importantly, although the UI overlap, we found the magnitude of the point estimate for the reduction in tuberculosis incidence per unit increase in BMI to be lower among people with HIV. If undernutrition causes tuberculosis through its effects on cell-mediated immunity (which has been termed nutritionally acquired immune deficiency syndrome),[9] this would be expected given that people with HIV have a competing cause of immune deficiency. Furthermore, we were able to characterise and confirm the same association both among people with diabetes, and in the general population cohorts which adjusted for diabetes. People with HIV and diabetes, who were underrepresented in the RATIONS trial, require specific consideration in future interventional research. Both groups are more likely to be eligible for tuberculosis preventive treatment, which may modify the effect of nutritional support; and nutritional interventions for people with diabetes need particularly careful design and evaluation as their nutritional needs and metabolism differ from the general population.

Our results can be used to inform modelling of the potential impact on tuberculosis incidence of changing nutritional status in populations.[59-61] This is particularly important in the context of climate change, which is expected to worsen food security and undernutrition through the effects of extreme weather events as well as changing temperatures and precipitation on crop yields, grassland quality, and oceans.[62-65] Importantly, the impacts of climate change on food systems and undernutrition are likely to disproportionately affect vulnerable groups in many of the countries with the highest tuberculosis burden, especially in Africa and South-East Asia.[62,63] It is therefore important to highlight that while our review represents a substantial increase in evidence from the 2009 review[11], we found no cohorts among the general population in the African Region and only two small cohorts of household contacts in South-East Asia (in India). In contrast, since the last review there have been several very large population-based cohort studies in the Western Pacific Region (especially in South Korea) and multiple cohort studies investigating tuberculosis incidence in people with HIV, mostly undertaken in the African Region.

Our results should also be used to inform WHO calculations of the PAF of tuberculosis due to undernutrition, which previously used an estimate of the relative risk informed by the 2009 review[11] of 3.2 comparing a BMI

of 16.0kg/m$^2$ versus 25.0kg/m$^2$.[2,66] The recent Cochrane review, which estimated a HR closer to two, was undertaken partly to inform revised PAF calculations but is likely to have underestimated the risk of undernutrition for two main reasons.[12] First, in its meta-analyses the review combined some studies which used different definitions of undernutrition, and, more frequently, used different comparator groups. Given the log-linear association between tuberculosis incidence and BMI, considering studies which compared a BMI of <18.5kg/m$^2$ versus 18.5-24.9kg/m$^2$ (or in some cases 18.5-22.9kg/m$^2$) the same as studies which compared <18.5kg/m$^2$ versus ≥18.5kg/m$^2$ is likely to have biased the results and underestimated the risk of undernutrition. In several of the studies included in the meta-analyses the researchers demonstrated an inverse association between tuberculosis incidence and BMI in their population (including several where the reference category for the analysis was defined as "normal weight"), but these were not considered in the subgroup analysis investigating a dose-response relationship.[16,22,23,25,27,32,43,51] Second, for the overall summary HR, the Cochrane review pooled together studies done in the general population in both adults and children with those done in people with HIV, diabetes, and other conditions (e.g. recent gastrectomy). This may have led to bias, in either direction, because the effect of undernutrition is likely to be different in these populations.

We aimed to address these limitations in our meta-analyses by using a stricter comparison in adults of underweight (BMI<18.5kg/m$^2$) versus not underweight (≥18.5kg/m$^2$); and disaggregating results wherever possible. Further strengths of our review are that we included two new studies not published at the time of the Cochrane review,[21,54] several other studies for which we were either provided data or able to access the original data to calculate required estimates;[35,36,45,49,55] and could include important cohorts in our BMI analysis that were not included in the Cochrane review because they didn't specifically report on the risk of being underweight or only provided unadjusted estimates.[24,28,29,33,34,47] This enabled inclusion of data from over three million people representing a range of populations and geographies. In our sensitivity analyses, we explored various analysis options, including using the same methodology as that which informed the previous PAF,[11,66] and that used in the Cochrane review.[12] Importantly, we believe that estimates of the PAF for undernutrition must account for the continuous nature of the exposure and the underlying distribution of BMI in the population. In populations in LMIC where underweight is common, the mean BMI among those who are underweight is likely to be lower than in populations from HIC where underweight is rare. These HIC were disproportionately represented in both our analyses and the Cochrane review; and thus, the true relative risk of undernutrition may be higher than our estimates suggest.

Our study has limitations. First, we specifically focussed on the adult population because of challenges in tuberculosis diagnosis among children and differences in anthropometric measures. Only four studies done only in children and adolescents were included in the Cochrane review and further research is required in this population using more standardised measures. Second, our adjusted analyses were limited to adjusting for the variables originally adjusted for in each study. No studies explicitly used causal inference methods to estimate the magnitude of the effect of nutritional status on tuberculosis and only one incorporated sampling weights and survey design specifications, which demonstrated a much higher risk of tuberculosis among people who were underweight.[32] Future studies should state the conceptual framework which informed the adjusted analysis (e.g. through presenting a directed acyclic graph) and consider using more advanced methodologies such as propensity score approaches to adjust for potential confounders. Finally, despite the

clarity of our results and the clinical and practical utility of using BMI as an indicator of tuberculosis risk, research is required to characterise the pathways through which a lower BMI increases the risk of tuberculosis, and, conversely, why a higher BMI decreases risks. This could include longitudinal studies measuring macro- and micro-nutritional indicators at several time points to more comprehensively characterise how changing nutritional status affects tuberculosis risk.

In conclusion, our updated review and analysis confirms and substantially extends previous research demonstrating the importance of nutritional status for tuberculosis. Given that the historical evidence on improved nutrition and reduced tuberculosis has now been complemented by robust prospective observational, interventional, and modelling evidence, the global tuberculosis community must rapidly ensure that social protection and other interventions to improve nutrition become an integral component of the global tuberculosis response.

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**Declaration of interests.** All authors declare that they have no conflict of interest in relation to this publication.

**Authors contributions.** All authors participated in the research, and the preparation of the manuscript, and all have reviewed and approved the manuscript as submitted and take public responsibility for it. The breakdown of contribution is as stated below:

**Study conception:** MJS, PJC, RC, RMGJH, CFM
**Literature review and data extraction:** MJS, PJC, CFM
**Data analysis:** MJS, CFM
**Data Interpretation:** MJS, PJC, RC, RMGJH, CFM
**Draft manuscript:** MJS, CFM
**Manuscript review and finalisation:** MJS, PJC, RC, RMGJH, CFM

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**Data sharing.** R scripts including the code and data used in these analyses will be uploaded to Github prior to publication.

**Table 1**. Characteristics of included studies classified by population group and ordered by income status and World Health Organization (WHO) region

| Study | Country income status | Country | WHO Region | Years of recruitment | Population | Total number in analysis | Average follow-up time (years) | Outcome | Ascertainment | Variables adjusted for when available | Inclusion for analysis* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **General population cohorts** | | | | | | | | | | | |
| Palmer et al. 1957[34] | HIC | USA | AMR | 1949-1951 | Male navy recruits aged 17-21 years | 68,754 | 4.0 | All TB | Annual chest radiography, contact screening, tuberculin surveys, and hospital records | Age and sex, and tuberculin reactivity implicitly adjusted for | BMI only |
| Edwards et al. 1971[33] | HIC | USA | AMR | 1958-1967 | Male navy recruits aged 17-21 years | 823,199 | 4.0 | All TB | Annual chest radiography, contact screening, tuberculin surveys, and hospital records | Age and sex, and tuberculin reactivity implicitly adjusted for | BMI only |
| Cegielski et al. 2012[32] | HIC | USA | AMR | 1971-1975 | People aged 25-74 participating in the National Health and Nutrition Examination Survey (NHANES 1) and associated follow-up study (NHEFS) | 14,189 | 15.8 | All TB | Interviews, medical records, death certificates | Age, sex, race/ethnicity, income, alcohol, smoking, place of birth, diabetes, urban/rural | Both BMI and underweight |
| Hemila et al. 1999[28] | HIC | Finland | EUR | 1985-1993 | Males aged 50-69 who smoked and were participating in a trial on the effect of vitamin C supplementation on cancer | 26,975 | 6.4 | All TB | National hospital discharge register | Age, sex, marital status, education, residential area, smoking, alcohol use, vitamin supplements | BMI only |
| Tverdal A. 1986[29] | HIC | Norway | EUR | 1963-1975 | People aged 15 years and over participating in the national mass radiography service | 1,717,655 | 12.0 | All TB, but only new cases | National TB surveillance system | No adjusted analyses available | BMI only |
| Leung et al. 2007[23] | HIC | Hong Kong | WPR | 2000 | People aged 65 years and over enrolled at 18 health centres for elderly populations | 42,116 | 5.0 | All TB | Death registry and TB notification registry | Age, sex, smoking, alcohol use, language, marital status, education, housing, work status, receiving public assistance, diabetes, cholesterol, cardiovascular disease, hypertension, | Both BMI and underweight |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | COPD, asthma, malignancy, recent weight loss, recent hospital admission, ADL scores | |
| Soh et al. 2019[26] | HIC | Singapore | WPR | 1993-1998 | People aged between 45 and 74 belonging to two of the major dialect groups of Chinese in Singapore | 50,398 | 16.9 | All TB | National TB surveillance system | Age, sex, year of recruitment, language, education, smoking, alcohol use, tea intake, energy intake, protein intake, cholesterol and fatty acids, vitamin A/C | Both BMI and underweight |
| Choi et al. 2021[19] (no diabetes) | HIC | South Korea | WPR | 2009 | People aged 20 years and over who participated in a national health screening exam in 2009 | 9,204,330 | 7.3 | All TB | Korean National Health Insurance system/rare intractable disease programme | Age, sex, smoking, alcohol use, physical activity, income, hypertension, dyslipidaemia | Both BMI and underweight |
| Cho et al. 2022[18] | HIC | South Korea | WPR | 2010 | People aged 20 years and over who participated in a national health screening exam in 2010 | 11,135,332 | 6.3 | All TB | Korean National Health Insurance system/rare intractable disease programme | Age, sex, smoking, alcohol use, exercise, income, hypertension, diabetes, dyslipidaemia | Both BMI and underweight |
| Kim et al. 2018[22] | HIC | South Korea | WPR | 2002-2006 | People aged 20-89 in 2007 who participated in national health screening exams between 2002 and 2006 | 301,081 | 6.4 | All TB | Korean National Health Insurance system/rare intractable disease programme | Age, sex, household income, smoking, alcohol use, diabetes | Both BMI and underweight |
| Yoo et al. 2021[27] | HIC | South Korea | WPR | 2009-2014 | People aged 66 who participated in national health screening exams between 2009 and 2014 | 1,245,640 | 6.5 | All TB | Korean National Health Insurance system/rare intractable disease programme | Age (implicitly), Sex, income, smoking , alcohol use, physical activity, anaemia, GFR, TUG test, diabetes, ischaemic heart disease, stroke, pulmonary disease | Both BMI and underweight |
| Lin et al. 2018a NHIS[25] | HIC | Taiwan | WPR | 2001-2009 | Adults with median age 42 who participated in cross-sectional national health surveys | 48,713 | 7.6 | Bacteriologically confirmed TB | National TB surveillance system | Age, sex, marital status, education, smoking, alcohol use, employment status, household income | Both BMI and underweight |
| Lin et al. 2018b NTC[25] | HIC | Taiwan | WPR | 2005-2008 | Adults with median age 51 who participated in a community-based voluntary health screening programme | 119,340 | 7.3 | Bacteriologically confirmed TB | National TB surveillance system | Age, sex, marital status, education, smoking, alcohol use | Both BMI and underweight |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Saunders et al. 2017[36] | LMIC | Peru | AMR | 2002-2006 | Household contacts aged 18 and over of people with pulmonary TB | 1,767 | 2.8 | All TB | Active case finding, prevalence surveys, and clinic registers | Age, sex, poverty, previous TB | Both BMI and underweight |
| Saunders et al. 2020[35] | LMIC | Peru | AMR | 2007-2015 | Household contacts aged 18 and over of people with all forms of TB | 11,605 | 2.9 | All TB | Active case finding, prevalence surveys, and clinic registers | Age, sex, poverty, previous TB | Both BMI and underweight |
| Aibana et al. 2016[30] | LMIC | Peru | AMR | 2009-2012 | Household contacts aged 18 and over of people with pulmonary TB | 7,606 | 1.0 | All TB | Active follow-up 2, 6, and 12 months after recruitment | Age, sex, poverty, diabetes, HIV, smoking, alcohol use, IPT | Both BMI and underweight |
| Paradakar et al. 2020[56] | LMIC | India | SEA | 2014-2017 | Household contacts aged 18 and over of people with pulmonary TB | 647 | 1.6 | All TB | Active follow-up after 6, 12 and 24 months | Age, sex, HIV, smoking, alcohol consumption, LTBI, index case age, index sex, index HIV, index smear/culture, household type, income, where index slept | Underweight only |
| Sinha et al. 2024[54] | LMIC | India | SEA | 2015-2019 | Household contacts of any age of people with pulmonary TB | 857 | 2.0 | All TB | Unknown | No adjusted analyses available | Underweight only |
| Chen et al. 2022[16] | LMIC | China | WPR | 2013 | People aged 15 years and over participating in a community TB screening cohort | 26,022 | 1.7 | All TB | Yearly active follow-up | Age, sex, ethnicity, marital status, previous TB, smoking, alcohol use, known diabetes | Both BMI and underweight |
| Cheng et al. 2020[17] | LMIC | China | WPR | 2013 | People aged 65 and over who participated in a baseline TB prevalence survey | 34,076 | 1.3 | Bacteriologically confirmed TB | Yearly active follow-up and National TB surveillance system | Age, sex, smoking | Both BMI and underweight |
| Jiang et al. 2024[21] | LMIC | China | WPR | 2016 | People aged 65 years and over participating in a basic health survey | 39,122 | 6.8 | All TB | National TB surveillance system | Age, sex, smoking, alcohol use, exercise | Both BMI and underweight |
| **People with HIV** | | | | | | | | | | | |
| Mupfumi et al. 2018[49] | LMIC | Botswana | AFR | 2008-2011 | People aged 18 years and over with and AIDS defining condition or a CD4 count <250 eligible for ART | 240 | 1.7 | All TB | Clinic visits at 1 month then every 3 months until week 96 | Hb | Underweight only |
| Dembele et al. 2010[41] | LMIC | Burkina Faso | AFR | 1998-2005 | People with HIV aged 15 years and over recorded in ART registers as | 1,284 | 2.3 | All TB | Clinic registers | Age, sex, WHO stage, CD4 count | Underweight only |

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| | | | | | commencing ART in four HIV treatment centres | | | | | | |
| Tchakounte Youngui et al. 2020[51] | LMIC | Burkina Faso, Senegal, and Ivory Coast | AFR | 2010-2016 | People with HIV aged 16 years and over who started ART and had at least 1 follow up visit | 5,773 | 0.8 | All TB | Clinic registers | Centre, age, sex, CD4 count, Hb | BMI only |
| Alemu et al. 2020[39] | LMIC | Ethiopia | AFR | 2013 | People with HIV aged 15 years and over newly registered at ART centres of seven public health facilities | 566 | 3.8 | All TB | Clinic registers | Sex, employment, marital status, family size, alcohol addiction, previous TB, functional status, WHO stage, CD4 count, Hb, ART, IPT, cotrimoxazole | Underweight only |
| Tiruneh et al. 2019[52] | LMIC | Ethiopia | AFR | 2009-2012 | People with HIV aged 18 years and over enrolled on ART at two health facilities in Western Ethiopia | 600 | 2.5 | Not specified | Clinic registers | Age, CD4 count, weight, WHO stage, functional status, cotrimoxazole, opportunistic infection, IPT | Underweight only |
| Ahmed et al. 2018[38] | LMIC | Ethiopia | AFR | 2010-2011 | People with HIV aged 15 years and over newly enroled in HIV care in government health facilities | 421 | 3.1 | All TB | Clinic registers | Marital status, family size, substance use, previous TB, opportunistic infection, bedridden, length of follow-up, WHO stage, Hb, CD4 count, IPT | Underweight only |
| Aemro et al. 2020[37] | LMIC | Ethiopia | AFR | 2014-2018 | People with HIV aged 15 years and over commencing ART in a referral hospital | 494 | 2.0 | All TB | Clinic registers | Previous TB, HIV disclosure, WHO stage, CD4 count, Hb, functional status, ART adherence, IPT | Underweight only |
| Nicholas et al 2011a[50] (pre-ART) | LMIC | Guinea, Kenya, Malawi, Mozambique, Nigeria, Uganda | AFR | 2006-2008 | People with HIV with median age 34 years enrolled in MSF-supported HIV programmes, pre-ART | 8,868 | 0.82 | All TB | Clinic registers | Setting, sex, previous TB, CD4 count | Underweight only |
| Nicholas et al 2011b[50] (during ART) | LMIC | Guinea, Kenya, Malawi, Mozambique, Nigeria, Uganda | AFR | 2006-2008 | People with HIV with median age 34 years enrolled in MSF-supported HIV programmes, during ART | 18,293 | 0.90 | All TB | Clinic registers | Setting, year, sex, age, prior ART, previous TB, CD4 count, time since ART | Underweight only |
| Chang et al. 2015[40] | LMIC | Nigeria | AFR | 2005-2010 | People with HIV aged 15 years and over commencing ART at the | 23,444 | 2.5 | All TB | Clinic registers | Sex, ART enrolment year, ART regimen, WHO stage, CD4 | Both BMI and underweight |

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| | | | | | Harvard/APIN PEPFAR program | | | | | count, viral load, Hb, ART adherence | |
| Hanrahan et al. 2010[43] | LMIC | South Africa | AFR | 2003-2008 | People with HIV aged 18 years and over identified through a clinic at the Perinatal HIV research unit | 3,456 | 1.4 | All TB | Active follow-up every 4-7 months, clinic registers, and death certificates | ART, CD4 count, IPT, income, employment, age, sex, years since HIV diagnosis | BMI only |
| Kufa et al. 2016[44] | LMIC | South Africa | AFR | 2011-2012 | People with HIV aged 18-45 with a recent CD4 count over 350 participating in a randomised trial of a TB vaccine | 621 | 0.9 | All TB | Active follow-up at 6 and 12 months | ART | Underweight only |
| Maro et al. 2010[46] | LMIC | Tanzania | AFR | 2001-2005 | People with HIV aged 18 years and over identified through HIV testing centres who were placebo recipients in a randomised trial of a TB vaccine | 979 | 3.2 | All TB | Clinic visits at 2, 4, and 6 months, and then every 6 months | No adjusted analyses available | Both BMI and underweight |
| Maokola et al. 2021[45] | LMIC | Tanzania | AFR | 2012-2016 | People aged 20 years and above enrolled in 315 care and treatment clinics for HIV who were not taking IPT | 75,812 | 1.7 | All TB | Clinic registers | Age, sex, ART, functional status, WHO stage | Both BMI and underweight |
| McDermid et al. 2013[47] | LMIC | The Gambia | AFR | 1986 onwards | People with HIV aged 18 years and over participating in an HIV clinical cohort based at MRC Gambia | 1,139 | 2.4 | All TB | Scheduled (unspecified frequency) or unscheduled clinic visits and household visits | No adjusted analyses available | Underweight only |
| Moore et al. 2007[48] | LMIC | Uganda | AFR | 2003-2005 | People aged 18 years and over eligible for ART participating in a randomised trial | 1,029 | 1.3 | All TB | Active case finding - weekly home visits | Age, sex, CD4 count, viral load, participated in a previous study, previous TB | Underweight only |
| Worodria et al. 2011[53] | LMIC | Uganda | AFR | Unknown | People with HIV aged 18 years and over eligible for ART at the Infectious Disease Institute in Kampala | 219 | 1.0 | All TB | Clinic visits at 2,4,8, and 12 weeks, then every 3 months | Age, sex, CRP, Hb, CD4 count, WHO stage | Underweight only |
| Batista et al. 2013[31] | LMIC | Brazil | AMR | 2007-2010 | People with HIV aged 18 years and over receiving treatment in two referral hospitals | 2,020 | 2.5 | All TB | Clinic registers, record linkage with TB surveillance system, deaths from TB from mortality surveillance system | LTBI and IPT, CD4 count, Hb, previous TB, literacy | Both BMI and underweight |
| Kyaw et al. 2022[57] | LMIC | Myanmar | SEA | 2011-2017 | People aged 15 years and over enrolled to the | 20,865 | 2.6 | All TB | Clinic registers | No adjusted analyses available | Both BMI and underweight |

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| | | | | | integrated HIV care programme | | | | | | |
| Salvadori et al. 2015[55] | LMIC | Thailand | SEA | 1999-2012 | People with HIV (adults, age unspecified) enrolled in the Program for HIV prevention and treatment | 1,682 | 7.0 | All TB | Clinic visits every 6 months | Age, sex, year, viral load, Hb, CD4 count | Both BMI and underweight |
| Choun et al. 2013[20] | LMIC | Cambodia | WPR | 2003-2010 | People aged 18 years and over enrolled in the HIV care program in a referral hospital | 2,930 | 2.7 | All TB occurring within the first six months of ART | Clinic registers | Previous TB, On TB treatment at enrolment, sex, age, Hb, CD4 count | Underweight only |
| **People with diabetes** | | | | | | | | | | | |
| Choi et al. 2021[19] | HIC | South Korea | WPR | 2009 | People aged 20 years and over who participated in a national health screening exam in 2009 | 883,573 | 7.1 | All TB | Korean National Health Insurance system/rare intractable disease programme | Age, sex, smoking, alcohol use, physical activity, income, hypertension, dyslipidaemia | Both BMI and underweight |
| Gedfew et al. 2020[42] | LMIC | Ethiopia | AFR | 2013-2017 | People with diabetes aged 18 years and over registered for chronic follow-up care in a referral hospital | 433 | 2.5 | Not specified | Clinic registers | Type of DM, previous TB, DM medications, alcohol use | Underweight only |
| Li et al. 2020[24] | LMIC | China | WPR | 2010-2015 | People with type 2 diabetes aged 35 years and over identified through the Shanghai Standardised Diabetes Management System | 234,418 | 3.6 | Pulmonary TB (positive smear, culture, or pulmonary lesions confirmed on pathology) | Shanghai TB surveillance system | No adjusted analyses available | Both BMI and underweight |

HIC=High-income countries; LMIC=Low- and middle-income countries; AMR=Region of the Americas; AFR=African Region; EUR=European Region; SEA= South-East Asian Region; WPR=Western Pacific Region; NHIS=National Health Interview Surveys; NTC=New Taipei City; TB=Tuberculosis; Hb=Haemoglobin; IPT=Isoniazid preventive treatment; LTBI=Latent TB infection; CRP=C reactive protein; ART=Antiretroviral therapy; MSF=Médecins sans Frontières; BMI=Body mass index

*Studies were either included in an analysis of the association between tuberculosis incidence and BMI; an analysis of the risk of incident tuberculosis in people who are underweight versus those not underweight, or both.

**Figure 1.** Study selection

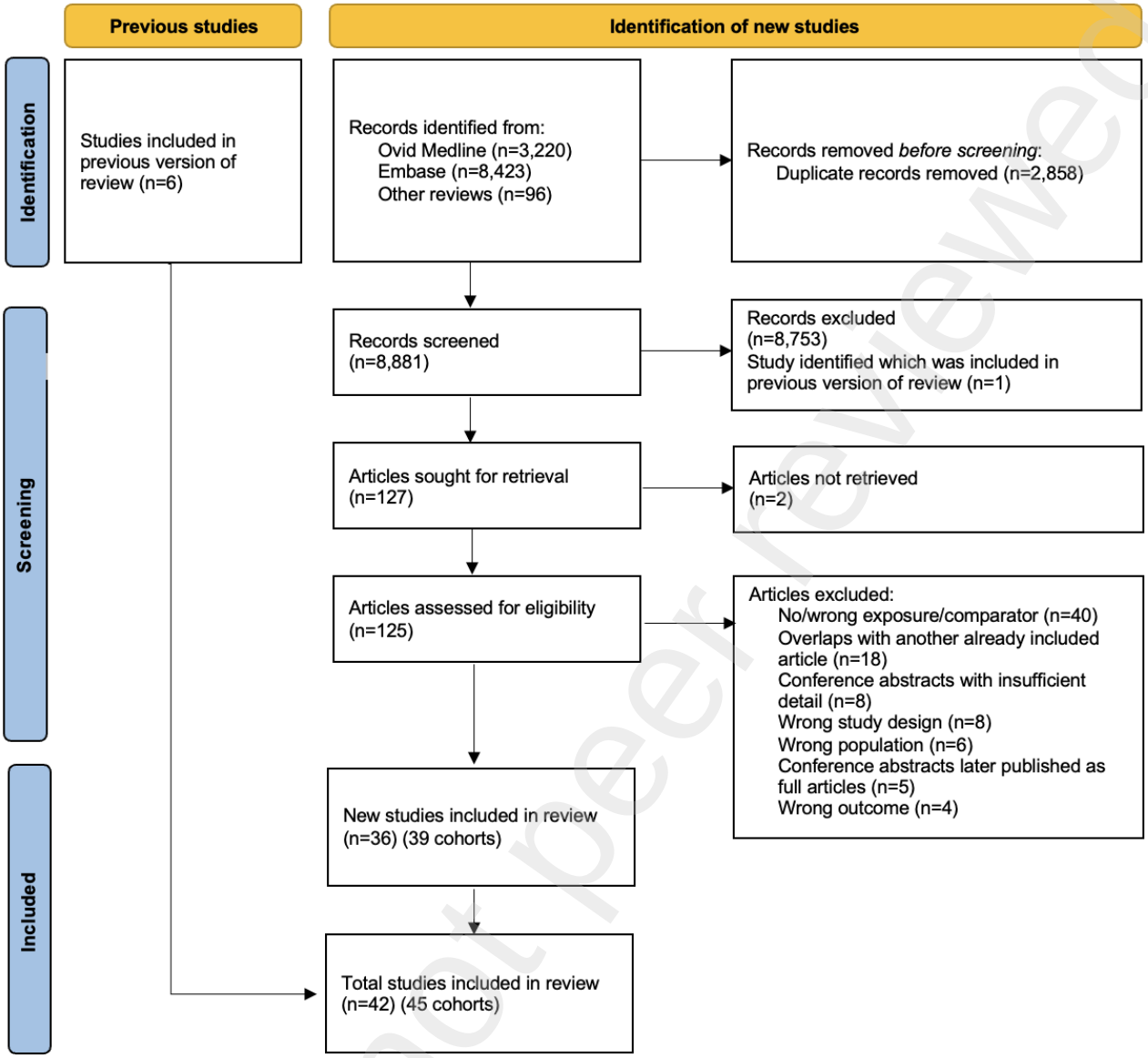
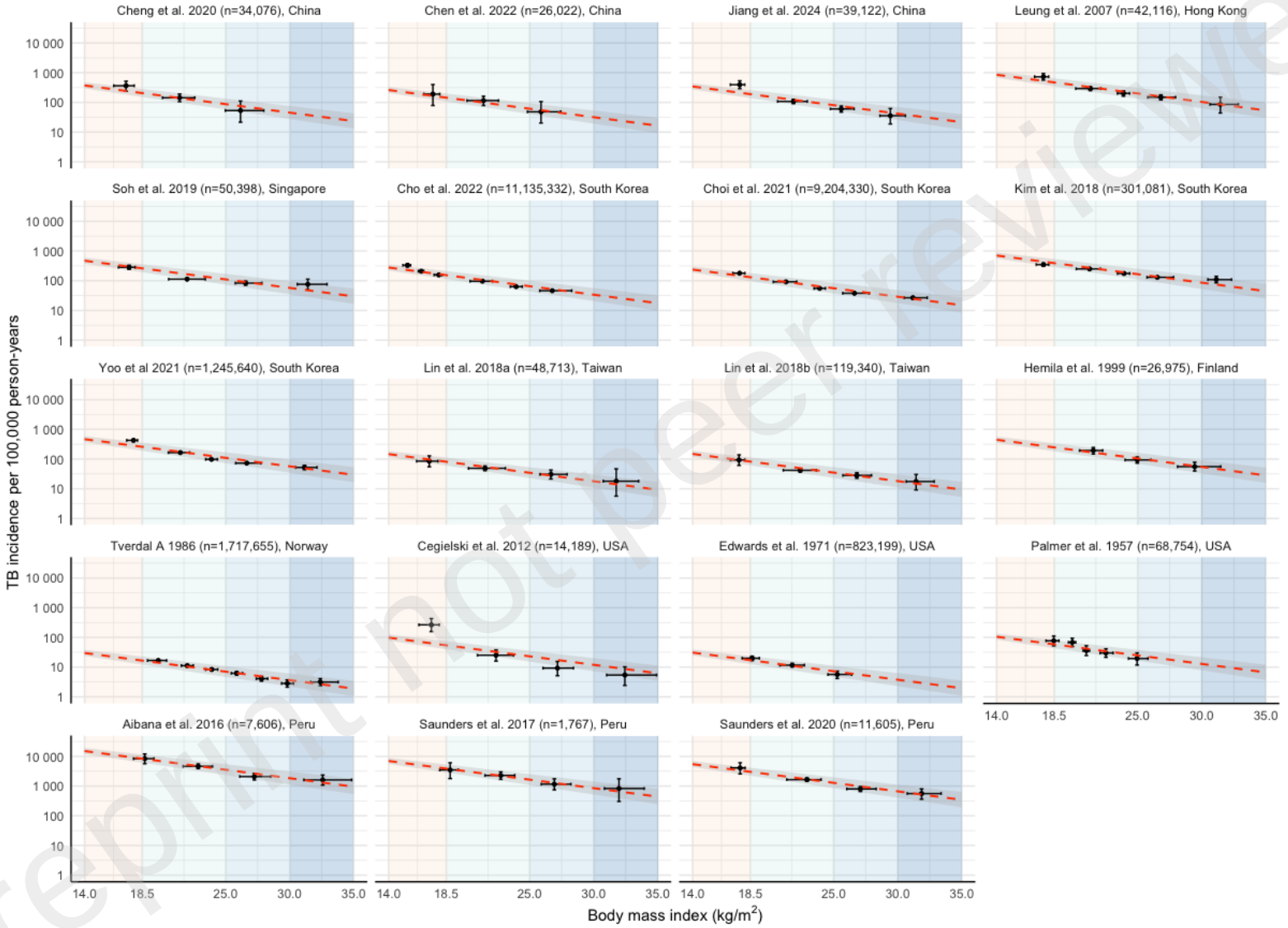


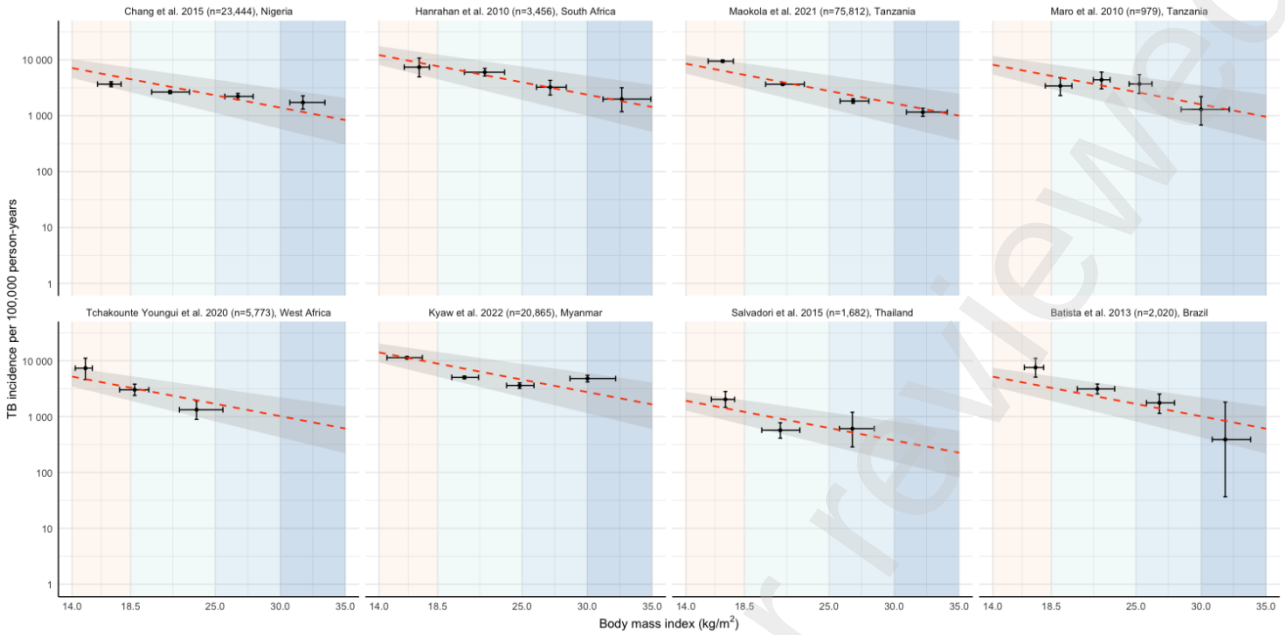
**Figure 2.** The association between tuberculosis (TB) incidence and body mass index in 19 general population cohorts (n=24,917,920)



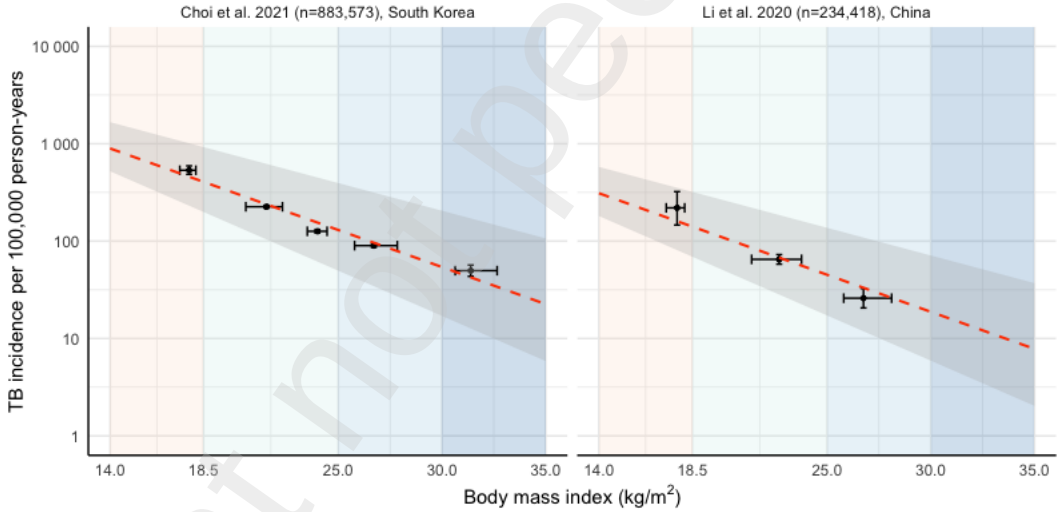

The red dashed line is the mean reduction in incidence per unit increase in body mass index across cohorts included in the analysis, with its 95% uncertainty interval in grey. This is superimposed on the resampled data from each study shown by the black points and error bars (see methods).

**Figure 3** The association between tuberculosis (TB) incidence and body mass index

**a)** Eight cohorts of people with HIV (n=134,031)




**b)** Two cohorts of people with diabetes (n=1,117,991)




The red dashed line is the mean reduction in incidence per unit increase in body mass index across cohorts included in the analysis, with its 95% uncertainty interval in grey. This is superimposed on the resampled data from each study shown by the black points and error bars (see methods).

**Figure 4.** Forest plot showing tuberculosis incidence rate ratios (IRR) for underweight (body mass index<18.5kg/m$^2$) versus not underweight (body mass index≥18.5kg/m$^2$) in 17 general population cohorts (n=22,282,841)

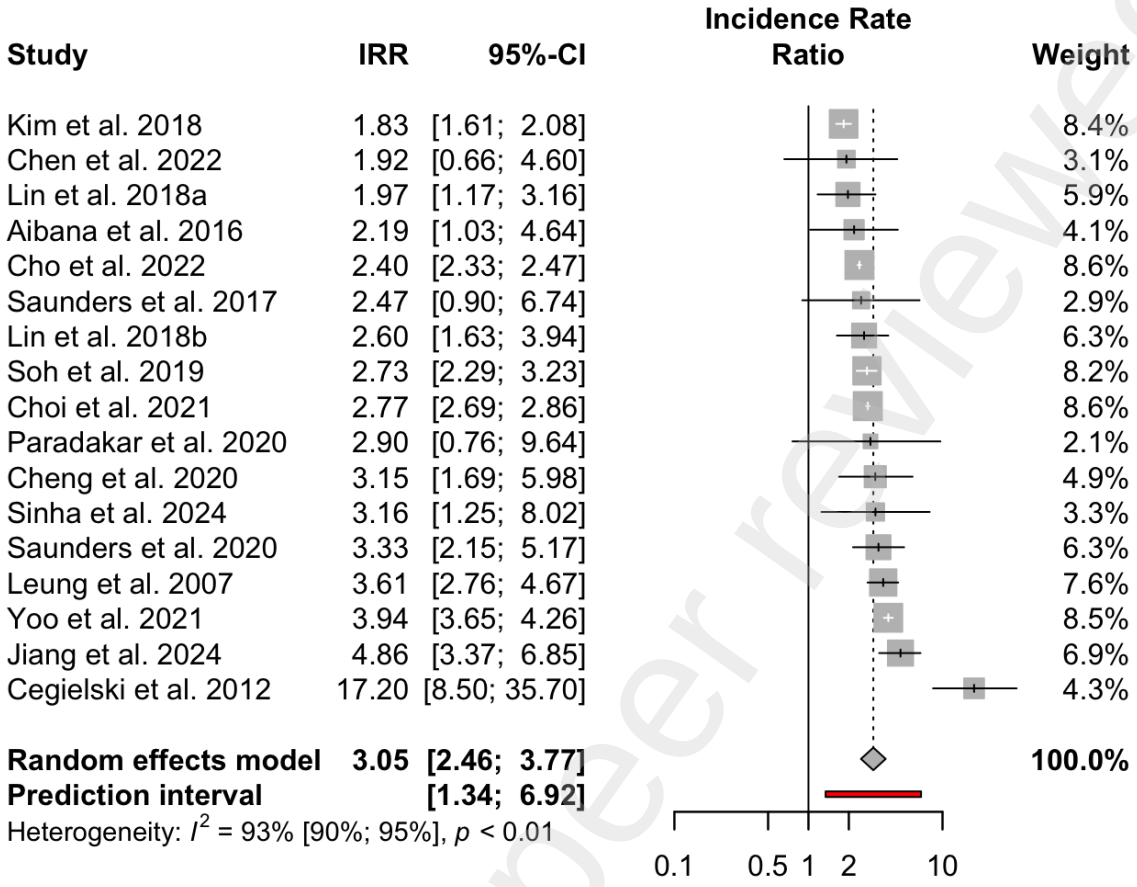
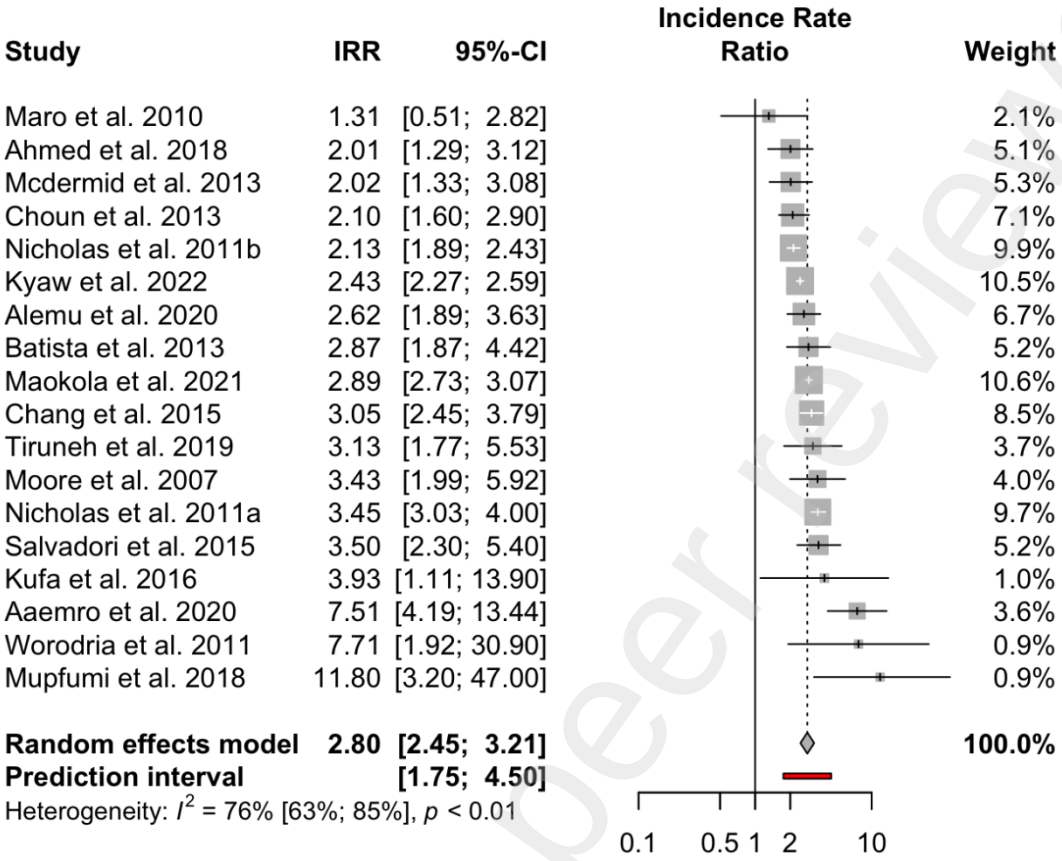
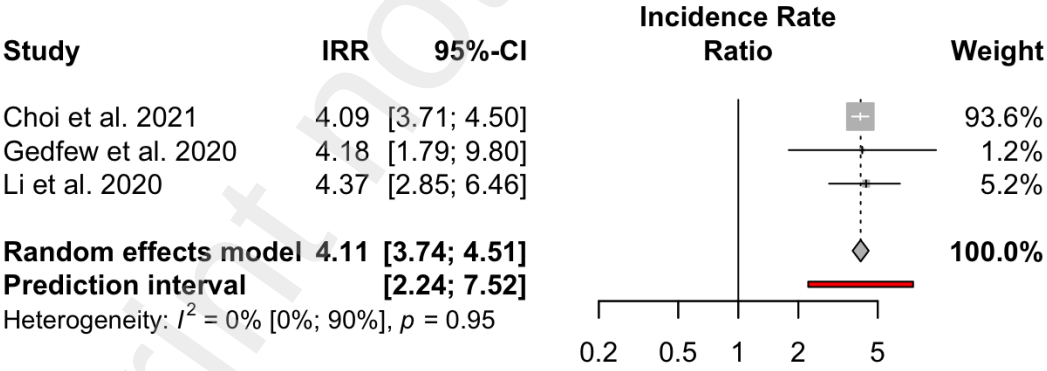


**Figure 5.** Forest plot showing tuberculosis incidence rate ratios (IRR) for underweight (body mass index<18.5kg/m$^2$) versus not underweight (body mass index ≥18.5kg/m$^2$)

**a)** 18 cohorts of people with HIV (n=160,222)




**b)** Three cohorts of people with diabetes (n=1,118,424)



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