Appendix: Impact of latent tuberculosis infection on health and well-being: a systematic review and meta-analysis

Appendix

Table S1 Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist

| Item No. | Recommendation | Reported on Manuscript Page No. |
|----------|----------------|---------------------------------|
| 1        | Problem definition | 1, 2                           |
| 2        | Hypothesis statement | Not applicable                  |
| 3        | Description of study outcome(s) | 3, 4                           |
| 4        | Type of exposure or intervention used | Not applicable                  |
| 5        | Type of study designs used | 4                              |
| 6        | Study population | 1, 4                           |
| 7        | Qualifications of searchers (eg, librarians and investigators) | 5                              |
| 8        | Search strategy, including time period included in the synthesis and key words | 3                              |
| 9        | Effort to include all available studies, including contact with authors | 4                              |
| 10       | Databases and registries searched | 3                              |
| 11       | Search software used, name and version, including special features used (eg, explosion) | Not applicable                  |
| 12       | Use of hand searching (eg, reference lists of obtained articles) | 4                              |
| 13       | List of citations located and those excluded, including justification | Figure 1                        |
| 14       | Method of addressing articles published in languages other than English | 4                              |
| 15       | Method of handling abstracts and unpublished studies | Not applicable                  |
| 16       | Description of any contact with authors | 4                              |
| 17       | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 4                              |
| 18       | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 4, 5                            |
| 19       | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | Not applicable                  |
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20 Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) Not applicable

21 Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results Not applicable

22 Assessment of heterogeneity 5

23 Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated 5

24 Provision of appropriate tables and graphics 7, 8, figure 2-4 and appendix figure S1-S20

Reporting of results should include

25 Graphic summarizing individual study estimates and overall estimate Figure 2-4

26 Table giving descriptive information for each study included 7, 8, Table 1

27 Results of sensitivity testing (eg, subgroup analysis) Not applicable

28 Indication of statistical uncertainty of findings 5, 10-12

Reporting of discussion should include

29 Quantitative assessment of bias (eg, publication bias) 17

30 Justification for exclusion (eg, exclusion of non-English language citations) Not reported

31 Assessment of quality of included studies 9

Reporting of conclusions should include

32 Consideration of alternative explanations for observed results 16

33 Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) Not applicable

34 Guidelines for future research 13, 15, 16

35 Disclosure of funding source 18
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Table S2 Databases and search terms used

| Database | Search terms |
|----------|--------------|
| Pubmed   | ("latent tuberculosis" infection OR LTBI OR tuberculosis prevent* OR inactive tuber*) AND ("quality of life" OR "health related quality of life" OR well-being OR health status OR disability OR "health outcome" OR "patient reported outcome" OR "quality adjusted life year" OR "disability adjusted life year" OR anxiety OR stress OR depression OR mobility OR self-care OR usual activities OR pain OR discomfort OR physical health OR physical well-being OR physical HRQoL OR physical functioning OR bodily pain OR general health OR vitality OR social functioning OR social health OR social well-being OR social HRQoL OR social relationship OR role emotion OR role physical OR "mental health" OR mental well-being OR mental HRQoL OR stigma OR psychosoc* OR psychological health OR fatigue OR emotional stress OR environmental health OR education OR employment OR income OR illness perception OR treatment perception OR morbidity OR mortality) |
| ProQuest | (latent tuberculosis infection OR LTBI OR tuberculosis prevent* OR inactive tuber*) AND ("quality of life" OR "health related quality of life" OR well-being OR health status OR disability OR "health outcome" OR "patient reported outcome" OR "quality adjusted life year" OR "disability adjusted life year" OR anxiety OR stress OR depression OR mobility OR self-care OR usual activities OR pain OR discomfort OR physical health OR physical well-being OR physical HRQoL OR physical functioning OR bodily pain OR general health OR vitality OR social functioning OR social health OR social well-being OR social HRQoL OR social relationship OR role emotion OR role physical OR "mental health" OR mental well-being OR mental HRQoL OR stigma OR psychosoc* OR psychological health OR fatigue OR emotional stress OR environmental health OR education OR employment OR income OR illness perception OR treatment perception OR morbidity OR mortality) |
| EMBASE   | ("latent tuberculosis'/exp OR 'inactive tuberculosis') AND ('quality of life'/exp OR 'hrql' OR 'health related quality of life' OR 'life quality' OR 'quality of life' OR 'health related quality of life' OR 'wellbeing'/exp OR 'well being' OR 'wellbeing' OR 'wellness' OR 'health status'/exp OR 'clinical state' OR 'health state' OR 'health status' OR 'health outcome' OR 'patient-reported outcome'/exp OR 'patient reported outcome measures' OR 'patient-reported outcome' OR 'patient-reported treatment outcome' OR 'patientreported outcome' OR 'self-reported outcome' OR 'self-reported patient outcome' OR 'self-reported treatment outcome' OR 'selfreported outcome' OR 'anxiety'/exp OR 'anxiety' OR 'depression'/exp OR 'central depression' OR 'clinical depression' OR 'depression' OR 'depressive disease' OR 'depressive disorder' OR 'depressive episode' OR 'depressive illness' OR 'depressive personality disorder' OR 'depressive state' OR 'depressive symptom' OR 'depressive syndrome' OR 'mental depression' OR 'parental depression' OR mobility OR 'self care'/exp OR 'usual activities' OR 'pain'/exp OR 'acute pain' OR 'deep pain' OR 'lightning pain' OR 'nocturnal pain' OR 'pain' OR 'pain response' OR 'pain syndrome' OR 'treatment related pain' OR 'discomfort'/exp OR 'physical health score'/exp OR 'physical well-being'/exp OR 'physical well-being' OR 'physical wellbeing' OR 'physical hrqol' OR 'physical functioning'/exp OR 'bodily pain'/exp OR 'general health'/exp OR 'vitality'/exp OR 'social functioning scale'/exp OR 'social health'/exp OR 'social well being'/exp OR 'social hrqol' OR 'social interaction'/exp OR 'social functioning' OR 'social interaction' OR 'social relation' OR 'social relationship' OR 'role emotion' OR 'role physical' OR 'mental health'/exp OR 'condition, mental' OR 'health, mental' OR 'mental care' OR 'mental condition' OR 'mental factor' OR 'mental health' OR 'mental help' OR 'mental service' OR 'mental state' OR 'mental status' OR 'mental status schedule' OR 'psychic health' OR |

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'psychological well-being'/exp OR 'mental well-being' OR 'mental wellbeing' OR 'psychological well being' OR 'psychological well-being' OR 'mental hrqol' OR 'psychological health'/exp OR 'stigma'/exp OR 'fatigue'/exp OR 'fatigue' OR 'tiredness' OR 'stress'/exp OR 'alarm reaction' OR 'stress' OR 'stress capacity' OR 'stress reaction' OR 'stress resistance' OR 'stress response' OR 'stress situation' OR 'stress tolerance' OR 'emotional stress'/exp OR 'emotional distress' OR 'emotional exhaustion' OR 'emotional pressure' OR 'emotional shock' OR 'emotional stress' OR 'emotional tension' OR 'stress, emotional' OR 'mental stress'/exp OR 'mental stress' OR 'mental stresses' OR 'mental tension' OR 'nervous stress' OR 'psychic stress' OR 'psychic tension' OR 'psycho-social stress' OR 'psycho-social stresses' OR 'psychologic stress' OR 'psychological stress' OR 'psychosocial stress' OR 'psychosocial stresses' OR 'stress, mental' OR 'stress, psychologic' OR 'stress, psychological' OR 'tension, mental' OR 'tension, psychic' OR 'environmental health'/exp OR 'environmental health' OR 'health, environmental' OR 'disability'/exp OR 'assessment, disability' OR 'chronic disability' OR 'disability' OR 'disability assessment' OR 'disability evaluation' OR 'disability evaluation' OR 'evaluation, disability' OR 'handicap' OR 'quality adjusted life year'/exp OR 'qaly' OR 'quality adjusted life year' OR 'quality adjusted life years' OR 'quality-adjusted life years' OR 'disability-adjusted life year'/exp OR 'daly' OR 'daly' OR 'daly' OR 'dals' OR 'disability-adjusted life year' OR 'disability-adjusted life years' OR 'moribundity'/exp OR 'disease frequency' OR 'disease incidence' OR 'disorder incidence' OR 'moribundity' OR 'moribundity pattern' OR 'moribundity rate' OR 'moribundity risk' OR 'rate, morbidity' OR 'mortality'/exp OR 'excess mortality' OR 'morbidity' OR 'mortality' OR 'mortality model' OR 'education'/exp OR 'baccalaureate education' OR 'child education' OR 'college admission test' OR 'education' OR 'education service' OR 'education, distance' OR 'education, nonprofessional' OR 'education, pharmacy' OR 'education, pharmacy, continuing' OR 'education, pharmacy, graduate' OR 'education, special' OR 'education, veterinary' OR 'educational measurement' OR 'intellectual training' OR 'internship, nonmedical' OR 'perceptorship' OR 'pharmacy residencies' OR 'preceptorship' OR 'school admission criteria' OR 'self-evaluation programmes' OR 'self-evaluation programs' OR 'training support' OR 'employment'/exp OR 'employment' OR 'employment growth' OR 'income'/exp OR 'income' OR 'illness perception'/exp OR 'treatment perception')

PsycInfo
(latent tuberculosis infection OR LTBI OR tuberculosis prevent* OR inactive tuber*)
AND ("quality of life" OR "health related quality of life" OR well-being OR health status OR disability OR "health outcome" OR "patient reported outcome" OR "quality adjusted life year" OR "disability adjusted life year" OR anxiety OR stress OR depression OR mobility OR self-care OR usual activities OR pain OR discomfort OR physical health OR physical well-being OR physical HRQoL OR physical functioning OR bodily pain OR general health OR vitality OR social functioning OR social health OR social well-being OR social HRQoL OR social relationship OR role emotion OR role physical OR "mental health" OR mental well-being OR mental HRQoL OR stigma OR psychosoc* OR psychological health OR fatigue OR emotional stress OR environmental health OR education OR employment OR income OR illness perception OR treatment perception OR morbidity OR mortality)

CINAHL Plus
(latent tuberculosis infection OR LTBI OR tuberculosis prevent* OR inactive tuber*)
AND ("quality of life" OR "health related quality of life" OR well-being OR health status OR disability OR "health outcome" OR "patient reported outcome" OR "quality adjusted life year" OR "disability adjusted life year" OR anxiety OR stress OR depression OR mobility OR self-care OR usual activities OR pain OR discomfort OR physical health OR physical well-being OR physical HRQoL OR physical functioning OR bodily pain OR general health OR vitality OR social functioning OR social health OR social well-being OR social HRQoL OR social relationship OR role emotion OR role physical OR "mental health" OR mental well-being OR mental HRQoL OR stigma OR psychosoc* OR psychological health OR fatigue OR emotional stress OR environmental health OR education OR employment OR income OR illness perception OR treatment perception OR morbidity OR mortality)
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relationship OR role emotion OR role physical OR “mental health” OR mental well-being OR mental HRQoL OR stigma OR psychosoc* OR psychological health OR fatigue OR emotional stress OR environmental health OR education OR employment OR income OR illness perception OR treatment perception OR morbidity OR mortality

Cochrane Central Register of Controlled Trials (CENTRAL) (latent tuberculosis infection OR LTBI OR tuberculosis prevent* OR inactive tuber*) AND (“quality of life” OR "health related quality of life" OR well-being OR health status OR disability OR "health outcome" OR "patient reported outcome" OR “quality adjusted life year” OR “disability adjusted life year” OR anxiety OR stress OR depression OR mobility OR self-care OR usual activities OR pain OR discomfort OR physical health OR physical well-being OR physical HRQoL OR physical functioning OR bodily pain OR general health OR vitality OR social functioning OR social health OR social well-being OR social HRQoL OR social relationship OR role emotion OR role physical OR “mental health” OR mental well-being OR mental HRQoL OR stigma OR psychosoc* OR psychological health OR fatigue OR emotional stress OR environmental health OR education OR employment OR income OR illness perception OR treatment perception OR morbidity OR mortality)

CHEST Journal (latent tuberculosis) AND (quality of life OR health outcome OR well-being OR mental OR physical OR social OR perception OR stigma OR environment)

European Respiratory Journal (ERJ) ("latent tuberculosis") AND (quality of life OR health related quality of life OR well-being OR health status OR health outcome OR patient reported outcome)

International Journal of Tuberculosis and Lung Disease (IJTLD) (latent tuberculosis) AND (quality of life OR health outcome OR well-being OR mental OR physical OR social OR perception OR stigma OR environment)
Appendix: Impact of latent tuberculosis infection on health and well-being: a systematic review and meta-analysis

Table S3 Summary of health outcomes measures reported by studies

| Instruments/Indicators | Studies | Follow-up intervals | Scores* | Without TB infection | Outcomes |
|------------------------|---------|---------------------|---------|----------------------|----------|
|                        |         |                     | LTBI    | TB                   |          |
| BDI                    | Marra et al., 2008 [1] | N/A | Differences in scores between individuals with LTBI and patients with active TB disease: Baseline- Mean difference: 3.98 (95% CI 224 to 5.71) |
|                        |         |                     |         |                      | N/A      | In individuals with LTBI, there was no difference in scores before and after treatment. In patients with active TB disease, the scores improved significantly after treatment. |
|                        |         |                     | 3 month-Mean difference: 2.60 (95% CI 1.04 to 4.16) |
|                        |         |                     | 6 month-Mean difference: 1.22 (95% CI -0.54 to 2.98) |
|                        | Unalan et al., 2008 [2] | N/A | 17.4±12.3 | 17.5±11.5 | 9.1±5.4 | Individuals with LTBI had comparable scores with patients having active TB disease, indicating similar risk of depression despite the asymptomatic manifestation of LTBI. |
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| EMIC for TB in Haitian Populations | Coreil et al., 2010 [3] | N/A | 25.1 | N/A | N/A | Majority of individuals with LTBI were unwilling to disclose the medical condition to friends and family as an indication of stigma. |
|-----------------------------------|-------------------------|-----|------|-----|-----|----------------------------------------------------------------------------|
| EQ-5D                             | Shedrawy et al., 2019* [4] | N/A | Median: 1 (IQR 0.79 to 1) | N/A | Median: 0.93 (IQR: 0.88 to 1) | Individuals with LTBI experienced stigma and fear of TB reactivation. HRQoL of individuals with LTBI was worse after treatment, hence the need to address psychosocial intervention. |
| Dion et al., 2004 [5]             | Baseline (Week 1) | Median: 84.8 (IQR 79.6 to 100) | Median: 79.6 (IQR 68.9 to 100) | N/A | | Individuals with LTBI had better HRQoL at baseline than patients with active TB disease. |
|                                   | Week 3                | Median: 100 (IQR 79.6 to 100) | Median: 100 (IQR 72.5 to 100) | N/A | | Patients with active TB disease had their HRQoL improved over time, comparable to individuals with LTBI, but results were not statistically significant. |
| HUI2                              | Guo et al., 2008* [6] | N/A | Mean: 0.93 (95% CI 0.90 to 0.95) | Mean: 0.85 (95% CI 0.80 to 0.89) | N/A | Individuals with LTBI had better health utilities than patients with active TB disease. |
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| Measure | Study Details | HUI3 | SF-36 | PCS | Note |
|---------|---------------|------|-------|-----|------|
|         |               | Mean: 0.90 | Median: 56.0 | Mean: 54.7 | Individuals with LTBI had better health utilities than patients with active TB disease. |
|         |               | (95% CI 0.86 to 0.94) | (IQR 52.4 to 58.8) | (95% CI 53.2 to 56.1) | |
|         |               | Mean: 0.76 | Median: 49.8 | Mean: 44.8 | |
|         |               | (95% CI 0.70 to 0.82) | (IQR 42.1 to 56.9) | (95% CI 42.1 to 47.5) | |
|         |               | N/A | N/A | N/A | 38% of individuals with LTBI were screened positive with mental distress. |
|         |               | N/A | N/A | N/A | |
|         |               | N/A | N/A | N/A | Individuals with LTBI had better HRQoL than patients with active TB disease. |
|         |               | N/A | N/A | N/A | HRQoL of individuals with LTBI and patients with active TB disease became more comparable at subsequent interviews, with substantial improvement observed in patients with active TB disease. |

References:

1. Marra et al., 2008
2. Dion et al., 2004
3. RHS-15
4. SF-36
5. Marra et al., 2008; Guo et al., 2008
6. HUI3
7. Guo et al., 2008
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|     | MCS | Mean: 50.3 (95% CI 48.5 to 52.0) | Mean: 40.1 (95% CI 37.1 to 43.1) | N/A | Individuals with LTBI had better HRQoL than patients with active TB disease. Older individuals with LTBI had poorer HRQoL than younger individuals with LTBI. |
|-----|-----|---------------------------------|---------------------------------|-----|-------------------------------------------------------------------------------------|
|     |     |                                 |                                 |     |                                                                                     |
|     |     | Unalan et al.,                  |                                 |     |                                                                                     |
|     |     | 2008 [2]                        |                                 |     |                                                                                     |
| PCS | N/A | 43.6±9.9                        | 41.8±10.1                       | 48.7±6.2 | Participants without TB infection had better HRQoL than individuals with LTBI and patients with active TB disease. In individuals with LTBI, PCS scores deceased with co-morbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease). In individuals with LTBI, lower PCS scores were observed in more elderly patients. |
| MCS | N/A | 38.4±11.4                       | 38.4±10.6                       | 42.5±10.0 | In individuals with LTBI, MCS scores increased with longer duration of sleep.          |
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|                | Bauer et al., 2015 [7] | Guo et al., 2008* [6] | Bauer et al., 2015* [8] |
|----------------|------------------------|-----------------------|------------------------|
| **PCS**        |                        |                       |                        |
| Baseline       | 50.3±1.1               | Mean: 0.82            | Mean: 0.91             |
|                | 6-month                 | Mean: 0.69±0.14       | Mean: 0.64±0.34        |
|                | 12-month                | Mean: 0.81±0.12       | Mean: 0.86±0.34        |
| **MCS**        |                        |                       |                        |
| Baseline       | 50.6±4.7               | Mean: 0.82 (95% CI 0.80 to 0.85) | Mean: 0.68 (95% CI 0.65 to 0.72) |
|                | 6-month                 | 51.5±3.9             | 0.83±0.23             |
|                | 12-month                | 51.3±4.5             | 0.84±0.12             |
| **SF-6D**      | Bauer et al., 2015* [8] |                       |                        |
| Baseline       | 0.81±0.11              | Mean: 0.82            | Mean: 0.91             |
|                | 6-month                 | Mean: 0.69±0.14       | Mean: 0.64±0.34        |
|                | 12-month                | Mean: 0.80±0.12       | Mean: 0.86±0.34        |

HRQoL of individuals with LTBI was comparable with participants without TB infection but better than patients with active TB disease.

Individuals with LTBI had lower mean health utilities scores than patients with active TB disease over 12 months, but not statistically significant.

LTBI treatment did not impose substantial impact on the health utilities.

Individuals with LTBI had better health utilities than patients with active TB disease.

Individuals with LTBI had lower mean SG utilities scores than
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| 12-month | 0.91±0.16 | 0.89±0.21 | 0.97±0.06 | patients with active TB disease, but not statistically significant. |
|----------|------------|------------|------------|-----------------------------------------------------------------|
| Dion et al., 2002 [9] Baseline | Median: 97.5 (IQR 97.5 to 100) | Median: 92.5 (IQR 75.0 to 97.5) | N/A | Individuals with LTBI had higher self-rated scores than patients with active TB disease, implying better self-evaluated health status. |
| SGRQ Pasipanodya et al., 2007 [10]; Miller et al., 2009 [11] | N/A | 10.0±14.4 | 24.0±23.0 | N/A | Individuals with LTBI had lower scores than patients with active TB disease, indicating better lung function in individuals with LTBI. Patients with active TB disease suffered from lung impairment even after treatment completion. Foreign-born participants had higher scores than local-born participants, indicating poorer lung function in foreign-born participants. |
| VAS Guo et al., 2008* [6] | N/A | Mean: 0.87 (95% CI 0.84 to 0.90) | Mean: 0.66 (95% CI 0.61 to 0.71) | N/A | Individuals with LTBI had higher scores than patients with active TB disease. |
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| Study                          | Baseline | Median: 90.0 (IQR 85.0 to 97.0) | Median: 80.0 (IQR 50.0 to 86.0) | N/A | Individuals with LTBI had higher self-rated scores than patients with TB disease, implying better self-evaluated health status. |
|-------------------------------|----------|---------------------------------|---------------------------------|-----|-----------------------------------------------------------------------------------------------------------------------------------|
| Lifetime expected QALY        | Miller et al., 2009 [11] | N/A                             | 67.43 QALYs                     | 64.68 QALYs | 69.11 QALYs | QALY lost from TB (owing to illness, impairment and death) due to impairment after microbiologic cure. Preventive care on LTBI could yield better health quality. |
| Cox Regression-Adjusted Mortality per 1000 Person-Years | Miller et al., 2015 [12] | N/A                             | 1.23 Person-Years (95% CI 0.72 to 1.74) | 8.79 Person-Years (95% CI 4.94 to 12.64) | N/A | Preventive care targeting on LTBI management may be an important approach to reduce the risk and repercussion of TB. |
| Regression-Adjusted Duration of Survival HR | Miller et al., 2015 [12] | N/A                             | HR: 5.7 (95% CI 5.2 to 6.3) | HR: 4.1 (95% CI 3.3 to 4.9) | N/A | Preventive care targeting on LTBI management may be an important approach to reduce the risk and repercussion of TB. |
| Semi-structured interview     | Jansson et al., 2020 [13] | N/A                             | N/A                             | N/A | N/A | Pregnant women with LTBI experienced panic and worries upon LTBI diagnosis due to |
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misperception and a lack of knowledge of LTBI. They were reluctant to reveal their status of diagnosis to friends and family due to stigma.

* Study data presented as health utilities value.

# Scores are presented in mean±standard deviation, otherwise as stated.

LTBI: latent tuberculosis infection; TB: tuberculosis; N/A: not applicable; IQR: Inter-quartile range; CI: confidence interval; HRQoL: health-related quality of life; VAS: Visual Analogue Scale; HUI2: Health Utilities Index Mark 2; HUI3: Health Utilities Index Mark 3; SG: Standard gamble tasks; SF-36: Short Form (36) Health Survey; PCS: physical component summary; MCS: mental component summary; SF-6D: Short-Form Six-Dimension; EQ-5D: EuroQol-5 dimensions; SGRQ: St George Respiratory Questionnaire; BDI: Beck depression inventory; RHS-15: Refugee health screener-15; EMIC: Explanatory Model Interview Catalogue; HR: hazard ratio; QALY: quality-adjusted life year.
### Table S4 Psychometric properties of health-related quality of life instruments and health utilities measures used in tuberculosis

| Instrument | Reliability | Validity |
|------------|-------------|----------|
|            | Internal consistency | Test-retest reliability | Content validity | Responsiveness |
| **BDI [2]** | Excellent in individuals with LTBI and patients with active TB disease; good in participants without TB infection. | Not tested | BDI has strong correlation with SF-36 MCS; moderately strong correlation with SF-36 PCS; and moderate to strong correlation with the eight domains of SF-36. | Not tested |
| **EQ-5D [5, 9]** | Not tested | Good agreement | EQ-5D has moderately strong correlation with VAS, PCS and SF-36 MCS; poor correlation with SG. | Not tested |
| **HUI2 [1]** | Not tested | Not tested | HUI2 has strong correlation with SF-6D, HUI3 and SF-36 PCS; moderate correlation with VAS and SF-36 MCS. | Not tested |
| **HUI3 [1]** | Not tested | Not tested | HUI3 has strong correlation with HUI2, SF-36 PCS and SF-6D; moderate correlation with VAS and SF-36 MCS. | Not tested |
| **SF-36 [2, 5, 7]** | SF-36 domains: Acceptable to excellent in patients with active TB disease and individuals with LTBI; questionable to good in participants without TB infection [2]. | Not tested | SF-36 PCS has moderately strong correlation with BDI; SF-36 MCS has strong correlation with BDI; and the eight domains of SF-36 have moderate to strong correlation with BDI [2]. | From the 2-to 4- month visits in HRQoL study, clinically meaningful improvement in mean PCS scores was observed (effect sizes ≥ 0.50). No significant change observed in LTBI cohorts [7].

Excellent agreement for MCS; moderate to good agreement in general [5]. SF-36 PCS has moderately strong correlation with EQ-5D and VAS, poor correlation with SG [5]. SF-36 MCS has moderate correlation with EQ-5D and VAS; poor correlation with SG [5].
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| HRQoL Measure | SG [9] | SGRQ [10] | VAS [6, 9] |
|--------------|--------|-----------|------------|
| SF-6D [6, 8] | Not tested | Not tested | Not tested |
| SG [9] | Good to excellent | Excellent agreement | Excellent agreement |
| SGRQ | Excellent | Excellent agreement | Excellent agreement |
| VAS | Not tested | Not tested | Not tested |

SF-6D has strong correlation with VAS, HUI2/3, SF-36 PCS and MCS [6].

From the baseline to the 1-month evaluation in health utility study, clinically meaningful improvement in mean SF-6D health utility scores among participants treated for TB disease (effect size = 0.5) was observed, primarily among women (effect size = 0.7). No significant change observed in LTBI cohorts [8].

HRQoL: health-related quality of life; VAS: Visual Analogue Scale; HUI2: Health Utilities Index Mark 2; HUI3: Health Utilities Index Mark 3; SG: Standard gamble tasks; SF-36: Short Form (36) Health Survey; PCS: physical component summary; MCS: mental component summary; SF-6D: Short-Form Six-Dimension; EQ-5D: EuroQol-5 dimensions; SGRQ: St George Respiratory Questionnaire; BDI: Beck depression inventory
### Table S5 Risk of bias assessment of the observational studies using the Newcastle-Ottawa Scale

| Question               | Selection | Comparability | Outcome | Total scores |
|------------------------|-----------|---------------|---------|--------------|
| Bauer et al. [7, 8]    | 1         | 1             | 2       | 1            | 0            | 8       |
| Coreil et al [3]       | 1         | 1             | 2       | 1            | NA           | NA      | 7       |
| Dion et al. [5, 9]     | 1         | 1             | 2       | 0            | 0            | 1       | 4       |
| Guo et al. [1, 6]      | 1         | 1             | 1       | 0            | 1            | 1       | 7       |
| Miller et al. [10, 11] | 1         | 1             | 1       | 1            | NA           | NA      | 6       |
| Miller et al. [12]     | 1         | 1             | 1       | 0            | 1            | NA      | 5       |
| Shedrawy et al. [4]    | 1         | 0             | 1       | 0            | NA           | NA      | 4       |
| Unalan et al. [2]      | 1         | 1             | 1       | 0            | NA           | NA      | 5       |

NA: not available
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Table S6 Critical Appraisal Skills Programme (CASP) checklist for qualitative study

| Qualitative study identified | No. | Study validity                                      | Yes | Can’t tell | No |
|------------------------------|-----|----------------------------------------------------|-----|------------|----|
| Jansson et al. [13]          | 1   | Was there a clear statement of the aims of the research? |     | /          |    |
|                              | 2   | Is a qualitative methodology appropriate?          |     | /          |    |
|                              | 3   | Was the research design appropriate to address the aims of the research? |     | /          |    |
|                              | 4   | Was the recruitment strategy appropriate to the aims of the research? |     | /          |    |
|                              | 5   | Was the data collected in a way that addressed the research issue? |     | /          |    |
|                              | 6   | Has the relationship between researcher and participants been adequately considered? |     | /          |    |

Findings

|   |                                           |
|---|-------------------------------------------|
| 7 | Have ethical issues been taken into consideration? | / |
| 8 | Was the data analysis sufficiently rigorous? | / |
| 9 | Is there a clear statement of findings? | / |

Value of the study

|   |                                           |
|---|-------------------------------------------|
| 10| How valuable is the research? | / |
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Figure S1 to S20

| Study or Subgroup | LTBI Mean | SD | Total | TB Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------|----|-------|---------|----|-------|--------|-----------------------------------|-----------------------------------|
| Bauer 2015        | 50.3      | 1.1 | 81    | 49.5    | 1.3| 33    | 23.5%  | 0.60 [0.30, 1.30]                  |                                   |
| Dion 2004         | 55.73     | 5.031| 25    | 49.6    | 11.96| 17    | 18.0%  | 6.13 [0.11, 12.15]                |                                   |
| Guo 2008          | 54.7      | 6.6529| 78    | 44.8    | 12.4416| 84    | 25.4%  | 3.36 [0.96, 12.94]                |                                   |
| Unalan 2008       | 43.63     | 9.89 | 106   | 41.79   | 10.06| 196   | 27.0%  | 1.84 [-0.50, 4.18]                |                                   |

Total (95% CI): 292 Mean difference: 4.36 [0.29, 8.42]

Heterogeneity: Tau² = 14.45; Chi² = 36.56, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.10 (P = 0.04)

Figure S1 Mean difference for SF-36 PCS between individuals treated for LTBI compared to patients treated for active TB disease.

| Study or Subgroup | LTBI Mean | SD | Total | TB Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------|----|-------|---------|----|-------|--------|-----------------------------------|-----------------------------------|
| Bauer 2015        | 50.6      | 4.7 | 81    | 47.2    | 6.5| 33    | 34.2%  | 3.40 [0.96, 5.84]                  |                                   |
| Guo 2003          | 50.3      | 7.9835| 78    | 40.1    | 13.824| 84    | 31.9%  | 10.20 [6.75, 13.65]                |                                   |
| Unalan 2008       | 38.43     | 11.42| 108   | 38.35   | 10.0| 186   | 33.9%  | 0.08 [-2.54, 2.70]                |                                   |

Total (95% CI): 267 Mean difference: 4.44 [-0.81, 9.69]

Heterogeneity: Tau² = 19.40; Chi² = 21.07, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 1.66 (P = 0.10)

Figure S2 Mean difference for SF-36 MCS between individuals treated for LTBI compared to patients treated for active TB disease.
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| Study or Subgroup | LTBI Mean | SD | Total | TB Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------|----|-------|---------|----|-------|--------|-------------------------------------|-------------------------------------|
| Bauer 2015        | 94.8      | 11.8| 103   | 76.6    | 23.8| 47    | 23.7%  | 18.20 [11.02, 25.38]              |                                      |
| Guo 2008          | 54.3      | 7.064| 78    | 41.2    | 14.2| 84    | 45.9%  | 13.10 [9.66, 18.54]              |                                      |
| Unalan 2006       | 75.37     | 23.52| 108   | 60.7    | 26.52| 190   | 30.4%  | 8.07 [2.89, 14.45]              |                                      |
| **Total**         | 289       |     |       | 327     |     |       | 100.0% | 12.96 [8.56, 17.37]              |                                      |

*Heterogeneity: Tau² = 7.92; Chi² = 4.16, df = 2 (P = 0.12); I² = 52%*
*Test for overall effect: Z = 5.77 (P < 0.00001)*

**Figure S3** Mean difference between SF-36 Physical Function (PF) domain for individuals treated for LTBI compared to patients treated for active TB disease.

| Study or Subgroup | LTBI Mean | SD | Total | TB Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|-----------|----|-------|---------|----|-------|--------|-------------------------------------|-------------------------------------|
| Bauer 2015        | 91.8      | 13.6| 103   | 62.8    | 33.4| 48    | 29.7%  | 29.20 [19.20, 39.20]              |                                      |
| Guo 2008          | 51.9      | 9.8706| 78    | 38.1    | 15.6672| 84    | 40.0%  | 13.80 [9.91, 17.69]              |                                      |
| Unalan 2006       | 42.59     | 41.62| 108   | 33.93   | 40.07| 190   | 30.3%  | 8.86 [-0.99, 18.81]              |                                      |
| **Total**         | 289       |     |       | 325     |     |       | 100.0% | 15.81 [6.95, 26.68]              |                                      |

*Heterogeneity: Tau² = 59.36; Chi² = 9.77, df = 2 (P = 0.009); I² = 60%*
*Test for overall effect: Z = 3.34 (P = 0.00008)*

**Figure S4** Mean difference for SF-36 Role Physical (RP) domain between individuals treated for LTBI compared to patients treated for active TB disease.
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| Study or Subgroup | Mean (LTBI) | SD | Total | Mean (TB) | SD | Total | Weight | Mean Difference (IV, Random, 95% CI) | Mean Difference (IV, Random, 95% CI) |
|-------------------|-------------|----|-------|-----------|----|-------|--------|-------------------------------------|-------------------------------------|
| Bauer 2015        | 87.8        | 21.4 | 86    | 71.7      | 29 | 38    | 24.7%  | 16.10 [5.83, 26.37]                  |                                      |
| Guo 2008          | 55.7        | 13.2011 | 78    | 50.1      | 12.9024 | 84    | 43.0%  | 5.60 [2.03, 9.17]                    |                                      |
| Unaian 2008       | 57.84       | 31.42 | 108   | 53.74     | 31.52 | 196   | 32.2%  | -0.90 [-8.29, 6.49]                  |                                      |
| **Total (95% CI)**| **272**     | **318** | **100.0%** | **318** | **100.0%** | **6.10 [-1.24, 13.43]** |                                      |

Heterogeneity: Tau² = 29.22, Ch² = 6.97, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.63 (P = 0.10)

**Figure S5** Mean difference for SF-36 Bodily Pain (BP) domain between individuals treated for LTBI compared to patients treated for active TB disease.

| Study or Subgroup | Mean (LTBI) | SD | Total | Mean (TB) | SD | Total | Weight | Mean Difference (IV, Random, 95% CI) | Mean Difference (IV, Random, 95% CI) |
|-------------------|-------------|----|-------|-----------|----|-------|--------|-------------------------------------|-------------------------------------|
| Bauer 2015        | 79.4        | 18.2 | 102   | 69.7      | 13.9 | 47    | 30.4%  | 9.70 [3.45, 15.95]                  |                                      |
| Guo 2008          | 52.5        | 7.9835 | 78    | 44.5      | 10.1376 | 84    | 38.5%  | 9.00 [5.20, 10.80]                  |                                      |
| Unaian 2008       | 47.85       | 26.21 | 106   | 50.45     | 23.32 | 196   | 31.2%  | -2.60 [-8.52, 3.32]                 |                                      |
| **Total (95% CI)**| **288**     | **327** | **100.0%** | **327** | **100.0%** | **5.21 [-1.50, 11.92]** |                                      |

Heterogeneity: Tau² = 29.42, Ch² = 11.17, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 1.52 (P = 0.13)

**Figure S6** Mean difference for SF-36 General Health (GH) domain between individuals treated for LTBI compared to patients treated for active TB disease.
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| Study or Subgroup | LTBI Mean | SD | Total | TB Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|------------------|-----------|----|-------|---------|----|-------|--------|----------------------------------|----------------------------------|
| Bauer 2015       | 71.5      | 15 | 100   | 59      | 22.3| 45    | 29.5%  | 12.60 [6.45, 19.75]               |                                   |
| Guo 2008         | 52.7      | 9.8706 | 78   | 44     | 13.824| 84   | 39.1%  | 8.70 [6.15, 12.25]               |                                   |
| Umaran 2006      | 44.07     | 25.47 | 108  | 45.03  | 25.13| 196   | 32.4%  | -0.90 [-0.91, 4.99]             |                                   |
| Total (95% CI)   | 286       | 325 | 100.0%| 6.71   | -0.35, 13.78 |   |        |                                   |                                   |

Heterogeneity: Tau² = 30.03; Ch² = 10.09, df = 2 (P = 0.003); I² = 80%

Test for overall effect: Z = 1.86 (P = 0.06)

**Figure S7** Mean difference for SF-36 Vitality (VT) domain between individuals treated for LTBI compared to patients treated for active TB disease.

| Study or Subgroup | LTBI Mean | SD | Total | TB Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|------------------|-----------|----|-------|---------|----|-------|----------------------------------|----------------------------------|
| Bauer 2015       | 90.1      | 16.7 | 102  | 49.5    | 38.2| 45    | 28.6%  | 4.60 [29.10, 52.10]               |                                   |
| Guo 2008         | 52.7      | 9.3141 | 78   | 39.5    | 14.7465 | 94  | 36.2%  | 13.20 [9.43, 16.97]              |                                   |
| Umaran 2006      | 67.30     | 29.34 | 108  | 00.43   | 28.88| 190   | 34.1%  | 6.90 [0.09, 13.77]               |                                   |
| Total (95% CI)   | 288       | 326 | 100.0%| 19.18   | 5.33, 33.03 |   |        |                                   |                                   |

Heterogeneity: Tau² = 134.14; Ch² = 24.81, df = 2 (P < 0.00001); I² = 92%

Test for overall effect: Z = 2.11 (P = 0.037)

**Figure S8** Mean difference for SF-36 Social Function (SF) domain between individuals treated for LTBI compared to patients treated for active TB disease.
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| Study or Subgroup | Mean | SD  | Total | Mean | SD  | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------|-----|-------|------|-----|-------|--------|-----------------------------------|-----------------------------------|
| Bauer 2015        | 88.4 | 16.9| 104   | 70.5 | 31.6| 48    | 29.4%  | 17.30 [8.21, 27.59]                |                                   |
| Guo 2009          | 50.7 | 9.31| 78    | 35   | 23.9929| 84    | 40.5%  | 15.70 [11.16, 23.24]               |                                   |
| Unalan 2006       | 42.21| 46.06| 108  | 40.65| 39.91 | 3.96  | 30.1%  | 1.56 [-7.64, 10.96]               |                                   |
| Total (95% CI)    | 290  | 326 | 100.0%| 12.10| 3.21, 20.99] |                                   |  12.10 [3.21, 20.99]               |                                   |

Heterogeneity: \( \tau^2 = 45.45 \), \( \chi^2 = 7.66, \) df = 2 (\( P = 0.02 \)), \( I^2 = 75\% \)
Test for overall effect: \( Z = 2.67 (P = 0.006) \)

**Figure S9** Mean difference for SF-36 Role Emotion (RE) domain between individuals treated for LTBI compared to patients treated for active TB disease.

| Study or Subgroup | Mean | SD  | Total | Mean | SD  | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------|-----|-------|------|-----|-------|--------|-----------------------------------|-----------------------------------|
| Bauer 2015        | 76.5 | 16.5| 101   | 68.3 | 20.6| 46    | 28.7%  | 8.30 [1.53, 15.07]                |                                   |
| Guo 2008          | 50.9 | 9.7576| 78    | 44.4 |11.9068| 84    | 31.8%  | 6.50 [3.15, 9.85]                |                                   |
| Unalan 2006       | 53.11| 22.33| 108   | 55.65| 21.17| 190   | 33.3%  | -2.54 [-7.89, 2.61]              |                                   |
| Total (95% CI)    | 287  | 326 | 100.0%| 4.01 [-2.32, 10.34] |                                   |                                   |  4.01 [-2.32, 10.34]               |

Heterogeneity: \( \tau^2 = 24.50 \), \( \chi^2 = 9.76, \) df = 2 (\( P = 0.009 \)), \( I^2 = 79\% \)
Test for overall effect: \( Z = 1.24 (P = 0.21) \)

**Figure S10** Mean difference for SF-36 Mental Health (MH) domain between individuals treated for LTBI compared to patients treated for active TB disease.
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Table 1: Mean difference for SF-36 Physical Component Scores (PCS) between individuals treated for LTBI compared to individuals without TB infection.

| Study or Subgroup | LTBI Mean | LTBI SD | LTBI Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|-------------------|-----------|---------|------------|--------------|------------|---------------|-----------------------------------|
| Bauer 2015        | 50.3      | 1.1     | 81         | 50.2         | 0.7        | 91            | 0.10 [0.18, 0.38]                 |
| Unalan 2008       | 43.63     | 9.89    | 198        | 40.74        | 6.21       | 196           | -5.11 [-7.17, -3.05]              |
| Total (95% CI)    | 189       | 287     | 100.0%     | 24 [1.91]    | df = 1     | 0.000001; P = 0.98% | Test for overall effect: Z = 0.92 (P = 0.36) |

Figure S11 Mean difference for SF-36 Physical Component Scores (PCS) between individuals treated for LTBI compared to individuals without TB infection.

Table 2: Mean difference for SF-36 Mental Component Scores (MCS) between individuals treated for LTBI compared to individuals without TB infection.

| Study or Subgroup | LTBI Mean | LTBI SD | LTBI Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|-------------------|-----------|---------|------------|--------------|------------|---------------|-----------------------------------|
| Bauer 2015        | 50.6      | 4.7     | 81         | 51.7         | 4.3        | 91            | -1.10 [-2.45, 0.25]                |
| Unalan 2008       | 38.43     | 11.42   | 196        | 42.45        | 9.89       | 196           | -4.02 [-6.59, -1.45]               |
| Total (95% CI)    | 189       | 287     | 100.0%     | 24 [1.91]    | df = 1     | 0.000001; P = 0.98% | Test for overall effect: Z = 1.83 (P = 0.10) |

Figure S12 Mean difference for SF-36 Mental Component Scores (MCS) between individuals treated for LTBI compared to individuals without TB infection.
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| Study or Subgroup | LTBI Mean | SD | Total | Control Mean | SD | Total | Mean Difference | Mean Difference |
|-------------------|-----------|----|-------|--------------|----|-------|----------------|----------------|
| Bauer 2015        | 94.8      | 11.8 | 103   | 96.4         | 7.4 | 108   | -1.60 [-4.27, 1.07] | -1.60 [-4.27, 1.07] |
| Unalan 2006       | 75.37     | 23.52 | 100   | 66.4         | 12.9 | 136   | -11.03 [-15.02, -6.24] | -11.03 [-15.02, -6.24] |
| Total (95% CI)    | 211       | 204 | 100.0% | 304          | 100.0% | -6.10 [-15.33, 3.13] | -6.10 [-15.33, 3.13] |

Heterogeneity: Tau² = 40.55; Chi² = 11.36, df = 1 (P = 0.0036); I² = 91%
Test for overall effect: Z = 1.29 (P = 0.20)

**Figure S13** Mean difference for SF-36 Physical Function (PF) domain between individuals treated for LTBI compared to individuals without TB infection.

| Study or Subgroup | LTBI Mean | SD | Total | Control Mean | SD | Total | Mean Difference | Mean Difference |
|-------------------|-----------|----|-------|--------------|----|-------|----------------|----------------|
| Bauer 2015        | 91.8      | 13.6 | 103   | 91.2         | 13.3 | 109   | 0.60 [-3.02, 4.22] | 0.60 [-3.02, 4.22] |
| Unalan 2006       | 42.59     | 41.62 | 108   | 65.05        | 37  | 196   | -22.46 [-31.86, -13.06] | -22.46 [-31.86, -13.06] |
| Total (95% CI)    | 211       | 305 | 100.0% | 305          | 100.0% | -10.50 [-33.09, 12.08] | -10.50 [-33.09, 12.08] |

Heterogeneity: Tau² = 252.66; Chi² = 20.11, df = 1 (P = 0.00001); I² = 96%
Test for overall effect: Z = 0.91 (P = 0.39)

**Figure S14** Mean difference for SF-36 Role Physical (RP) domain between individuals treated for LTBI compared to individuals without TB infection.
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Figure S15 Mean difference for SF-36 Bodily Pain (BP) domain between individuals treated for LTBI compared to individuals without TB infection.

Figure S16 Mean difference for SF-36 General Health (GH) domain between individuals treated for LTBI compared to individuals without TB infection.
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**Figure S17** Mean difference for SF-36 Vitality (VT) domain between individuals treated for LTBI compared to individuals without TB infection.

**Figure S18** Mean difference for SF-36 Social Function (SF) domain between individuals treated for LTBI compared to individuals without TB infection.
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Figure S19 Mean difference for SF-36 Role Emotion (RE) domain between individuals treated for LTBI compared to individuals without TB infection.

Heterogeneity: Tau² = 0.80, Chi² = 6.45, df = 1 (P = 0.01); I² = 34%
Test for overall effect: Z = 0.58 (P = 0.57)

Figure S20 Mean difference for SF-36 Mental Health (MH) domain between individuals treated for LTBI compared to individuals without TB infection.
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