

# TANDEM

## TB treatment outcomes among patients with diabetes: Review update and research gaps

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# Tuberculosis treatment outcomes among patients with diabetes

- In 2011, a review including 33 studies found that diabetes worsens the treatment outcome among TB patients, **but emphasised the low quality of the evidence available**
  - *[Baker et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Public Health 2011 9:81]*
- Since then, many more studies have emerged on this topic including some better designed studies from large TB national control programmes
- We are updating this systematic review with newer studies – work still in progress

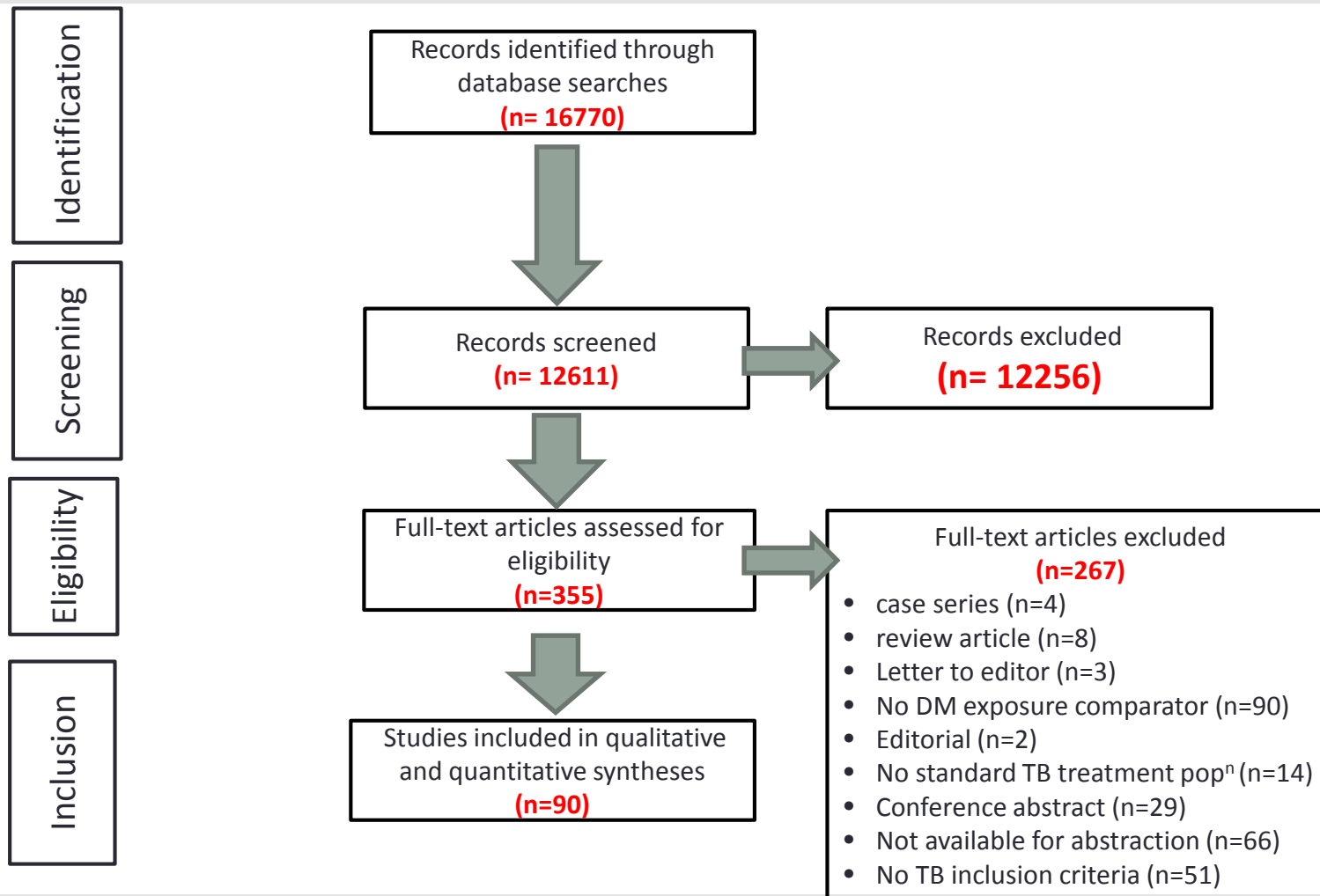
# Searching for Studies

- Sensitive search strategy used including terms for outcomes and risks
- PubMed, EMBASE and regional databases e.g. LILACS and WHO Regional libraries, Cochrane Libraries, citation searches of previous reviews also
  - ***TB AND DM***
  - ***TB AND Risk factors OR Treatment Outcomes [and synonyms]***
- Sensitive search attempts to reduce risk of bias from identifying only studies which mention diabetes in the title or abstract [or MeSH headings]

## Inclusion Criteria, Data extraction, Analysis

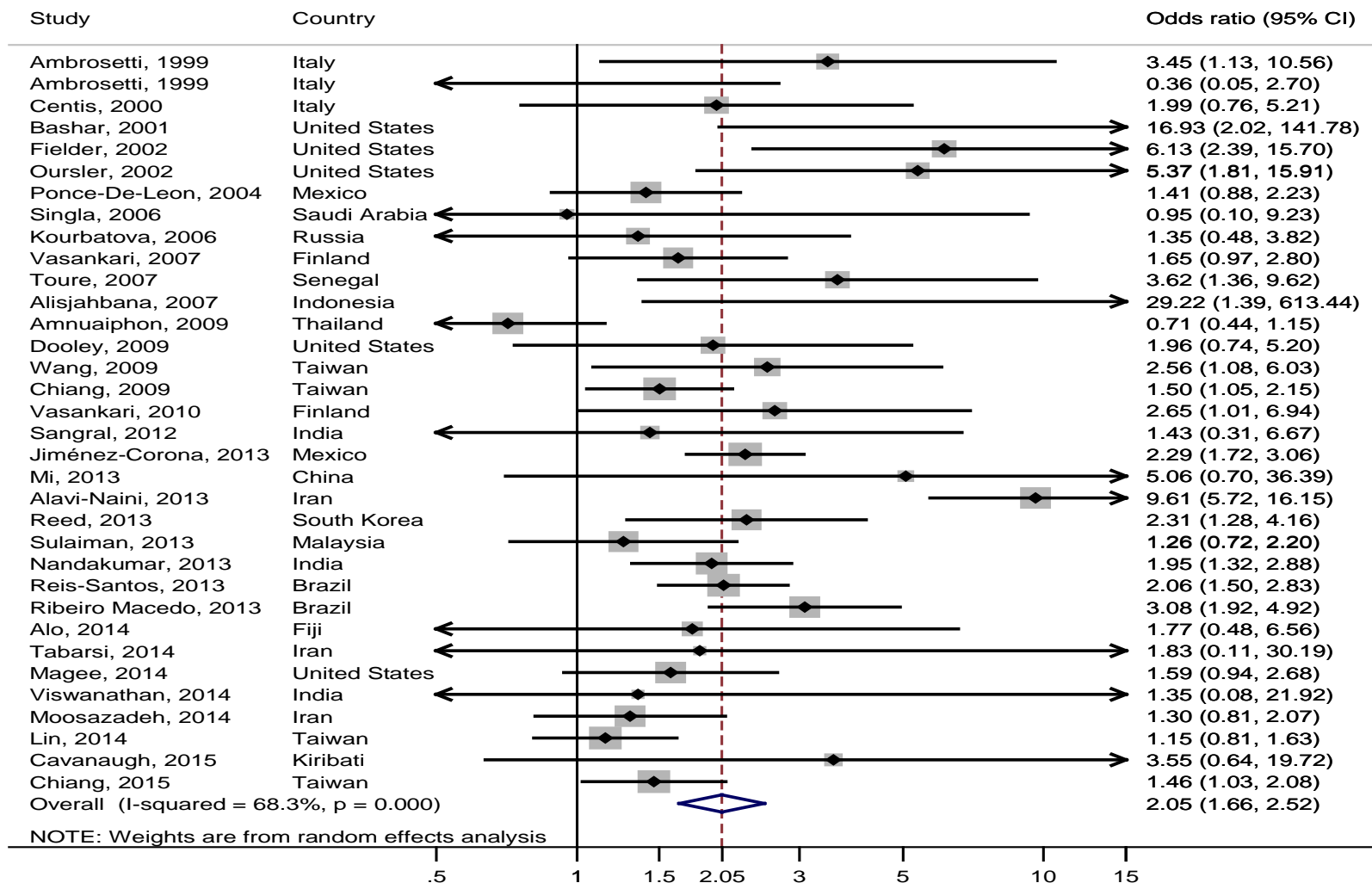
- Assessing studies for eligibility, data extraction and quality assessment all done by two independent researchers (CUG, PH, FP or JC)
- All case-control and cohort studies included regardless of language
  - **Observational studies – showing associations**
- Main exclusions were of MDRTB and severely ill  
(cohorts of TB patients with MDRTB at baseline, TB patients in intensive care)
- Time period: 1980-2015
- Data extracted on study design and study characteristics, key treatment outcomes, aspects of study quality – WHO criteria outcomes)
  - **Failure, cure, death, relapse, recurrence**
  - **Also MDRTB, 2 month conversion**
- **Random effects meta-analysis due to expected heterogeneity**

# Study Selection process



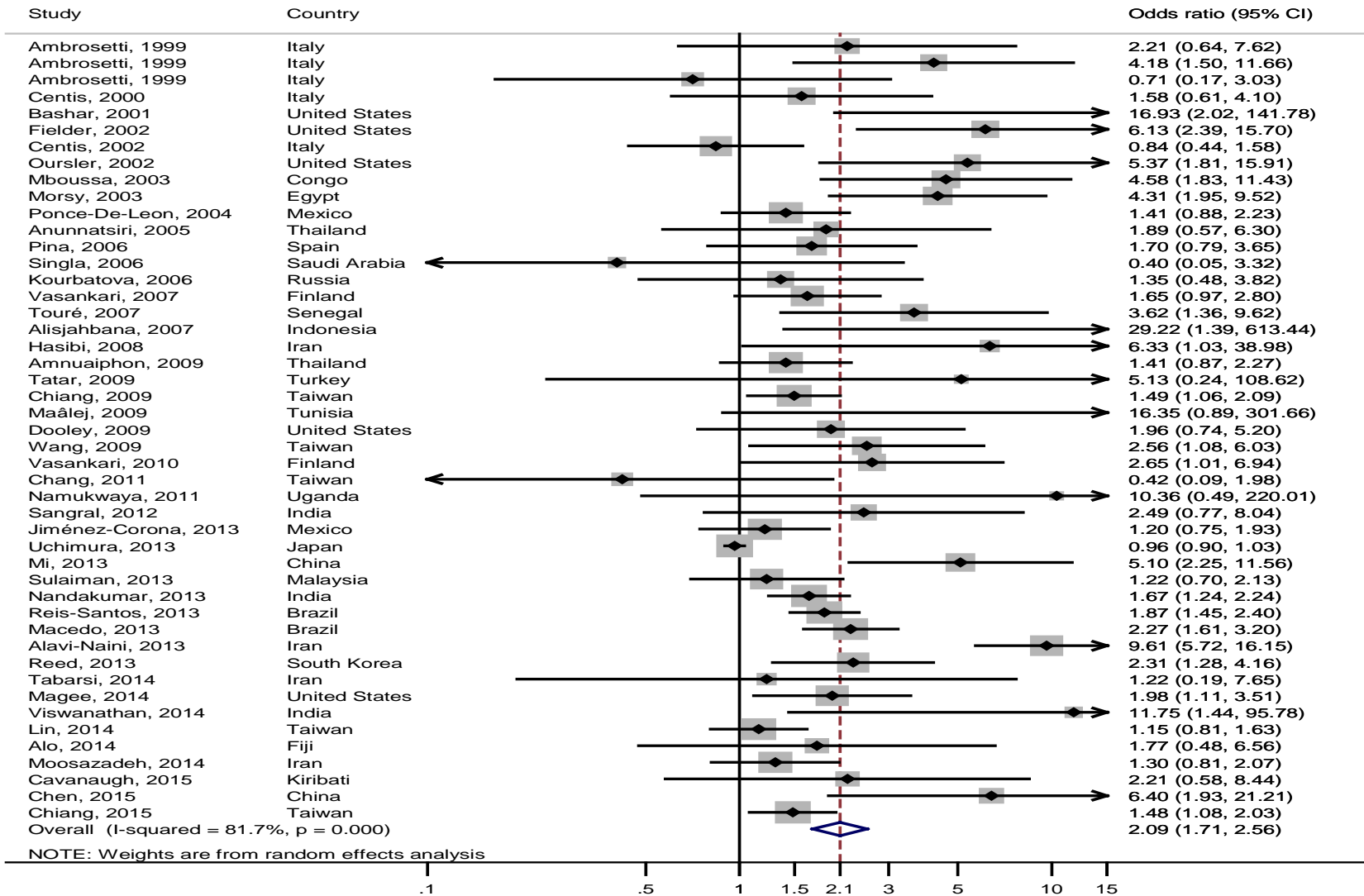
FINAL NUMBER OF STUDIES INCLUDE ABOUT 90 – may change slightly as double checking of some foreign language papers continues

# Key Outcomes - death



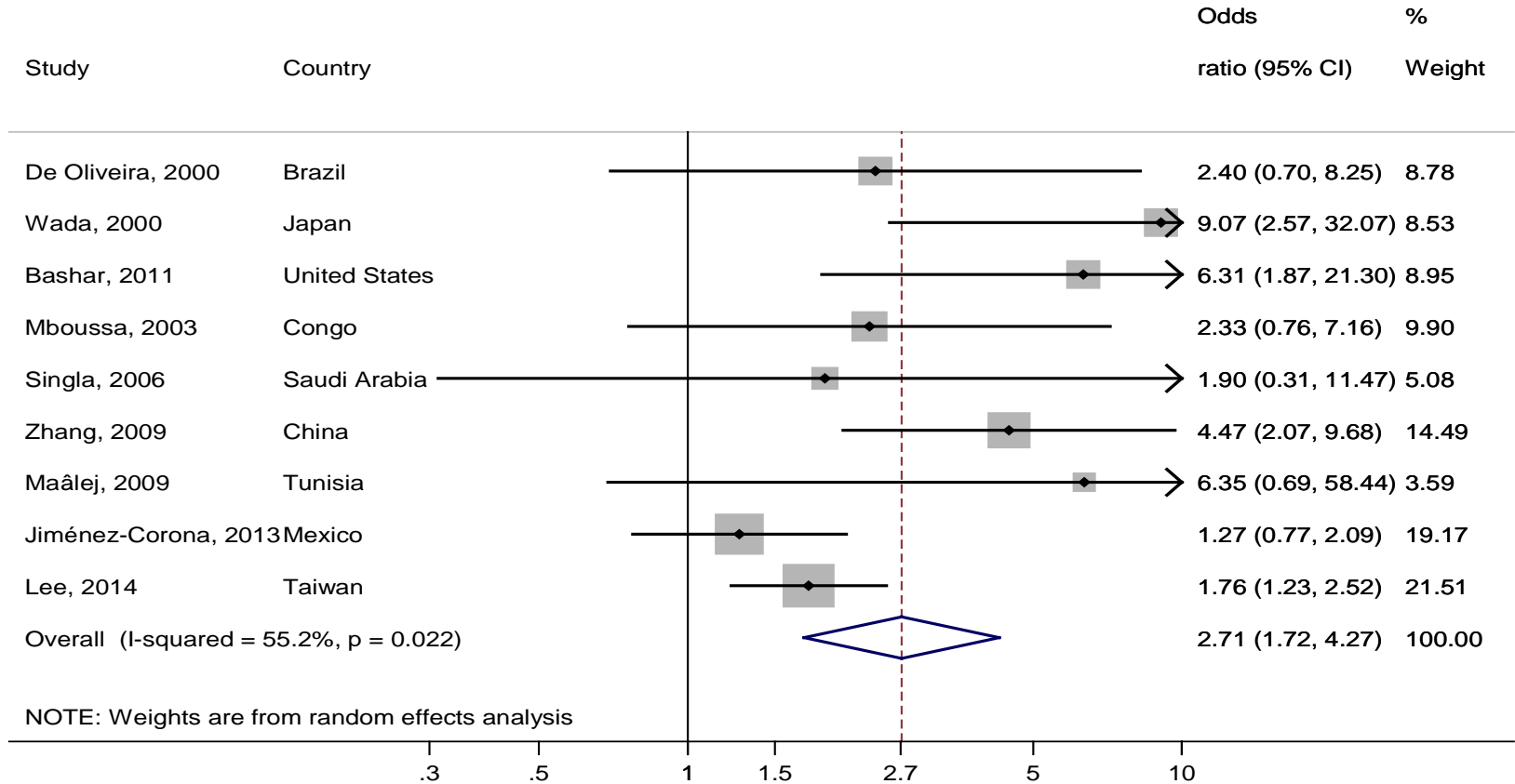
DM associated with a doubling of risk of mortality

# Death and treatment failure



... And a doubling of odds of death or treatment failure

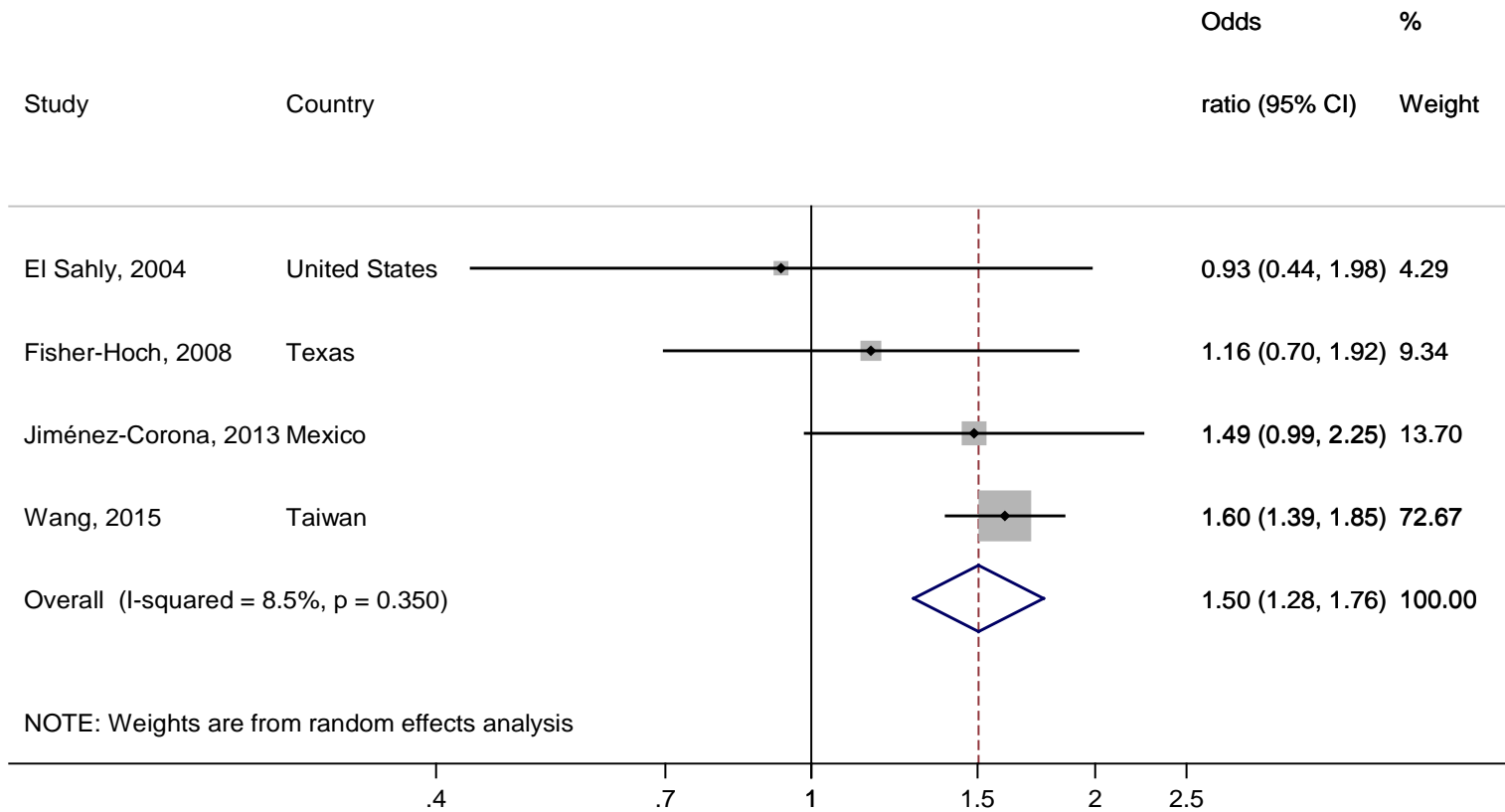
# Relapse



**DM associated with 2.7 fold increased risk of TB relapse**

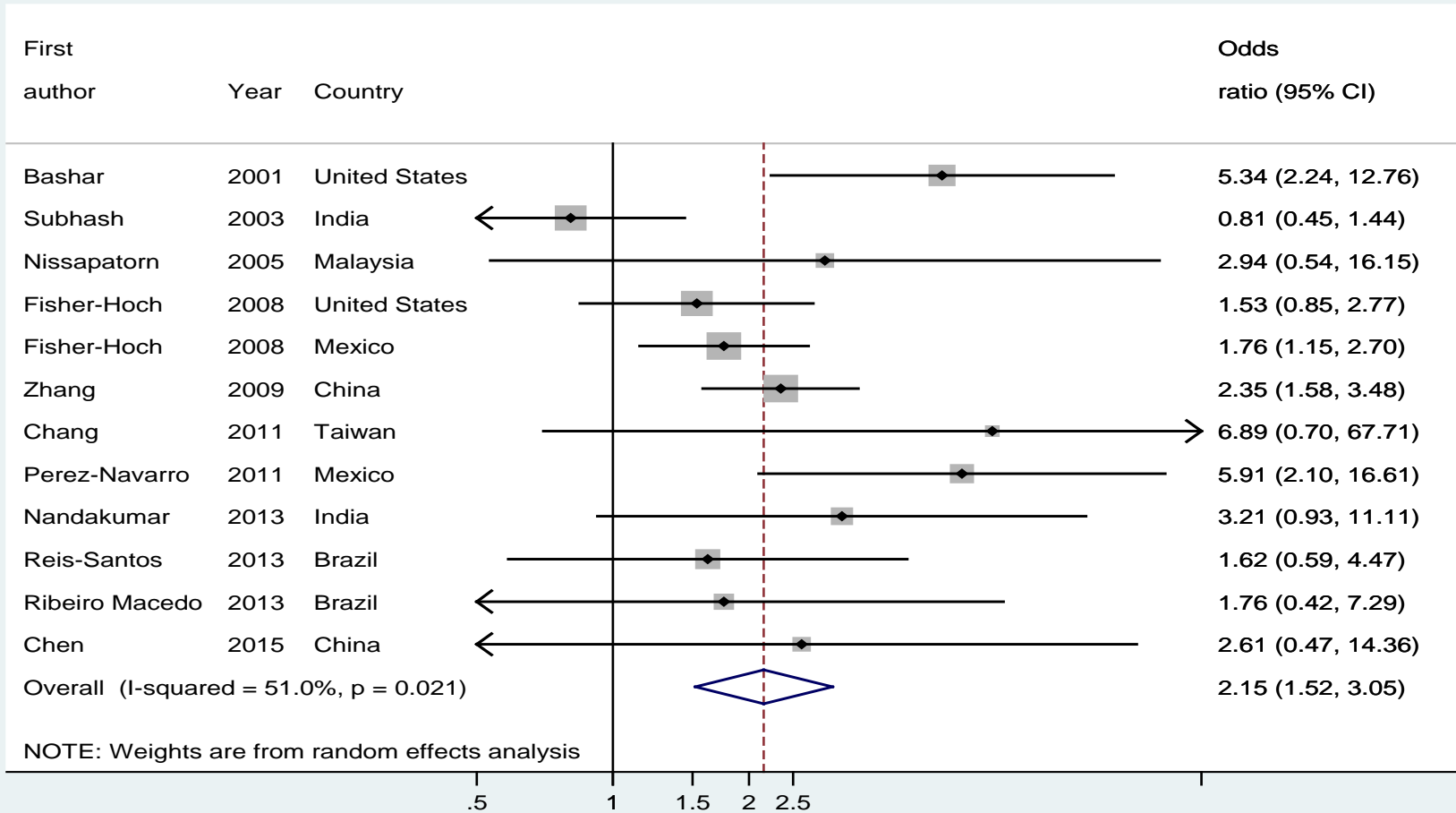


# Recurrence

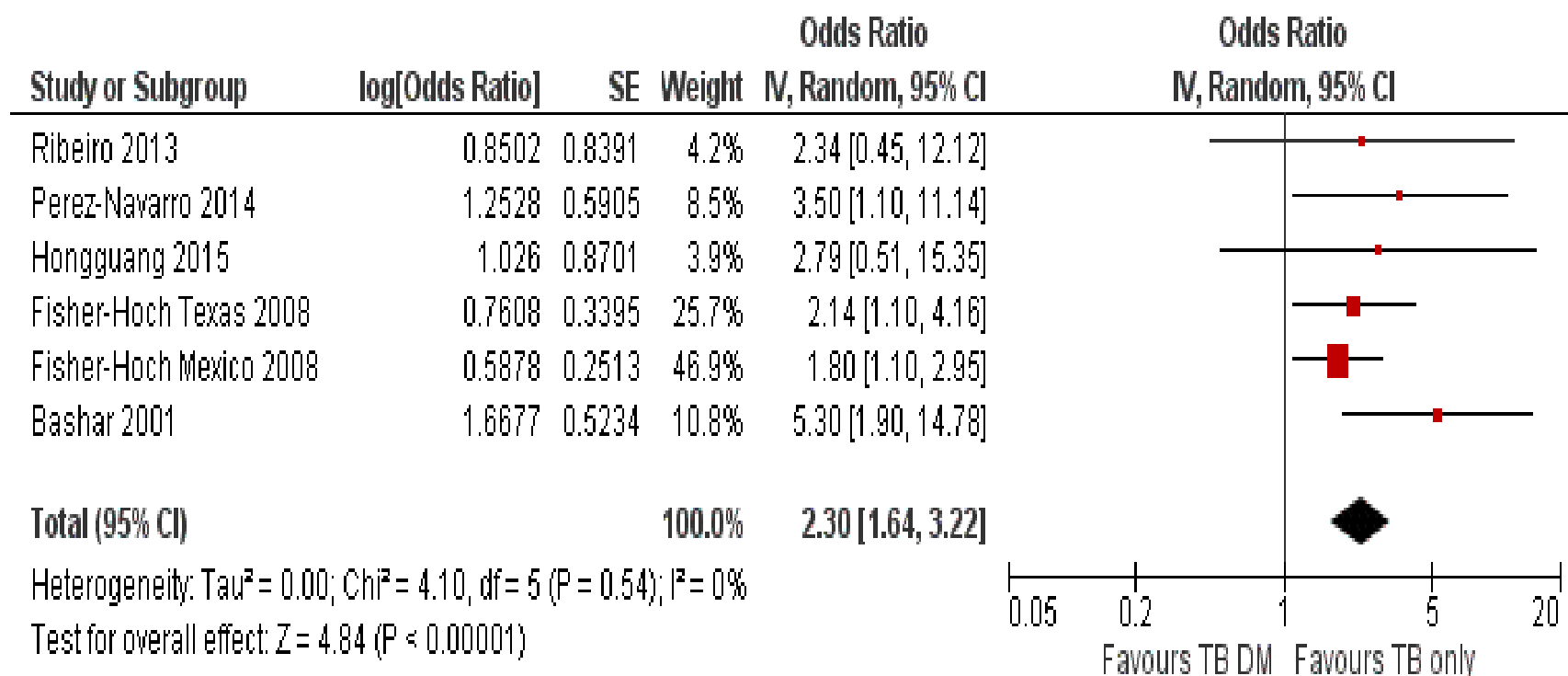


**DM associated with 50% increased risk of TB recurrence**

# MDRTB – all studies



# MDRTB – adjusted estimates only



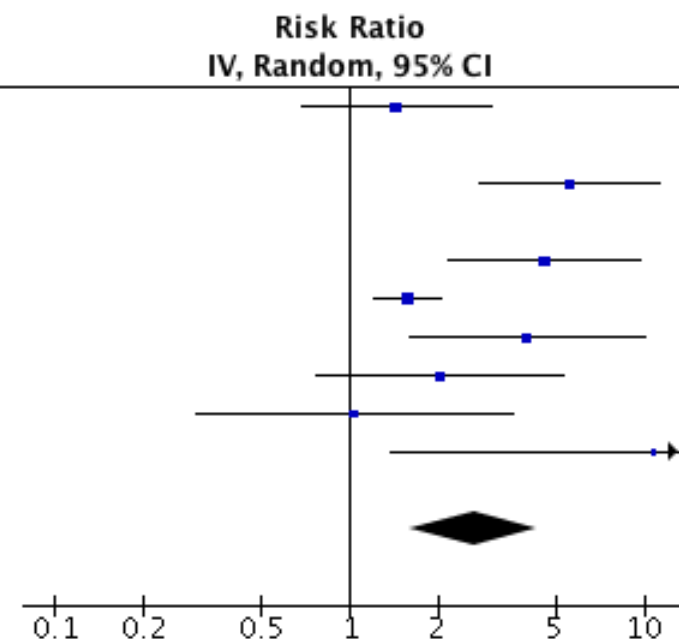
Adjustments vary, but most studies are adjusted for Hx TB, Age and Sex

## Double high burden: TB & DM

- Based on the Top Ten countries/territories for number of adults with DM (International Diabetes Foundation) and high TB-burden countries (based on WHO TB Report)
- Most of the studies are after 2010

# Risk of Death and Failure TB-DM vs TB : Countries with double high burden

Study or Subgroup	TB-DM		TB		Weight	Risk Ratio
	Events	Total	Events	Total		IV, Random, 95% CI
Alisjahbana 2007	8	94	32	540	14.2%	1.44 [0.68, 3.02]
Anunnatsiri 2005	4	38	11	188	0.0%	1.80 [0.60, 5.35]
Hongguang 2015	15	182	14	944	14.6%	5.56 [2.73, 11.31]
Mboussa 2003	13	32	13	100	0.0%	3.13 [1.62, 6.03]
Mi 2013	12	97	13	483	14.1%	4.60 [2.16, 9.77]
Nandakumar 2013	74	677	148	2127	19.9%	1.57 [1.20, 2.05]
Orofino 2012	4	14	21	294	12.1%	4.00 [1.59, 10.09]
Sangral 2012	4	23	24	280	11.6%	2.03 [0.77, 5.35]
Viswanthan 2013	4	96	6	149	9.0%	1.03 [0.30, 3.57]
Viswanthan 2014	8	89	1	120	4.5%	10.79 [1.37, 84.69]
<b>Total (95% CI)</b>		<b>1272</b>		<b>4937</b>	<b>100.0%</b>	<b>2.63 [1.61, 4.29]</b>



Total events 129 259  
Heterogeneity:  $\tau^2 = 0.30$ ;  $\chi^2 = 22.37$ ,  $df = 7$  ( $P = 0.002$ );  $I^2 = 69\%$   
Test for overall effect:  $Z = 3.86$  ( $P = 0.0001$ )

## Further analyses

- Work still in progress – meta-regression to explore heterogeneity in terms of
  - Region
  - TB / DM burden
  - Control of confounding
  - Methods of measurement
  - Other aspects of study design and quality
  - Diabetes control (rarely reported)

# Main “quality” issues

- **Control of confounding** - key confounders e.g. age, sex & HIV status
- Some studies may be over-adjusted e.g. adjusting for smear conversion at 2-3 months (**likely on pathway?**)
- Longer term follow-up studies [relapse, reinfection and development of MDRTB in TB-DM patients] mostly use regression analyses but these are usually not appropriate due to **competing risks**— survival analyses preferable
- Confusion around study design - case-control vs retrospective cohort studies
- **Misclassification** – DM status based on self-report or medical records which may underestimate the prevalence of diabetes & true association
- Conversely DM screening at time of acute TB disease could be associated with **stress hyperglycaemia** particularly if based on single glucose measurement
- Few studies report on any “DM variables” e.g. BMI, anthropometry, DM control, DM treatment and co-morbidities, DM duration
  - ----**SO TANDEM DATA CAN STILL ADD SUBSTANTIALLY TO THIS KNOWLEDGE BASE**

# What is “new” compared with previous systematic review

- Risks of death or treatment failure are slightly higher than previous estimates (**2 fold increase for TB-DM patients**)
  - May be higher in high burden countries
- Increased **recurrence risk and relapse** - possibly underestimated due to non-optimal analytical methods
- Increasing evidence that **MDRTB** is associated with diabetes (studies have limitations, but some adjusted for history of TB)
- Limited improvement in study design, reporting and analysis
- ***What about other infections and infection outcomes among patients with diabetes?***

Diabetes and infection: assessing the association with glycaemic control in population-based studies Jonathan Pearson-Stuttard, S Blundell, T Harris, D Cook, [Julia Critchley](#). Lancet Diabetes and Endocrinology 2016 Feb Volume 4(2): 148-158



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- **The statements made herein are solely the responsibility of the authors**