Undernutrition and Risk of Tuberculosis: Updated Meta-Analysis

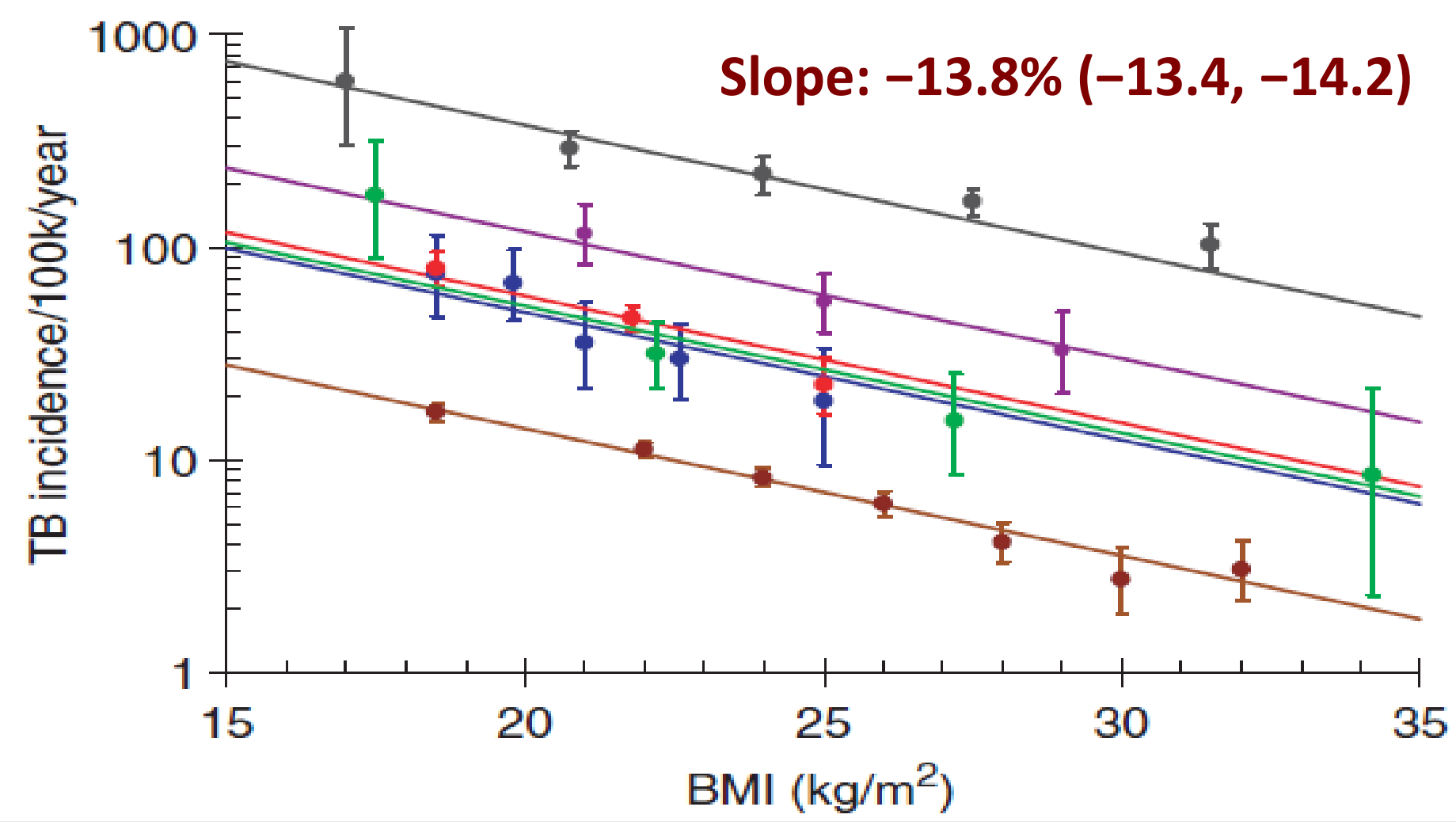
Peter Cegielski, MD, MPH

Senior Scientist, Emory Tuberculosis Center

Department of Epidemiology, Rollins School of Public Health

Emory University, Atlanta, Georgia, USA

Lönnroth 2010: A consistent log-linear relationship between tuberculosis incidence and body mass index



Color code:

gray, Leung

purple, Hemila

red, Edwards

green, Cegielski

blue, Palmer

brown, Tverdal

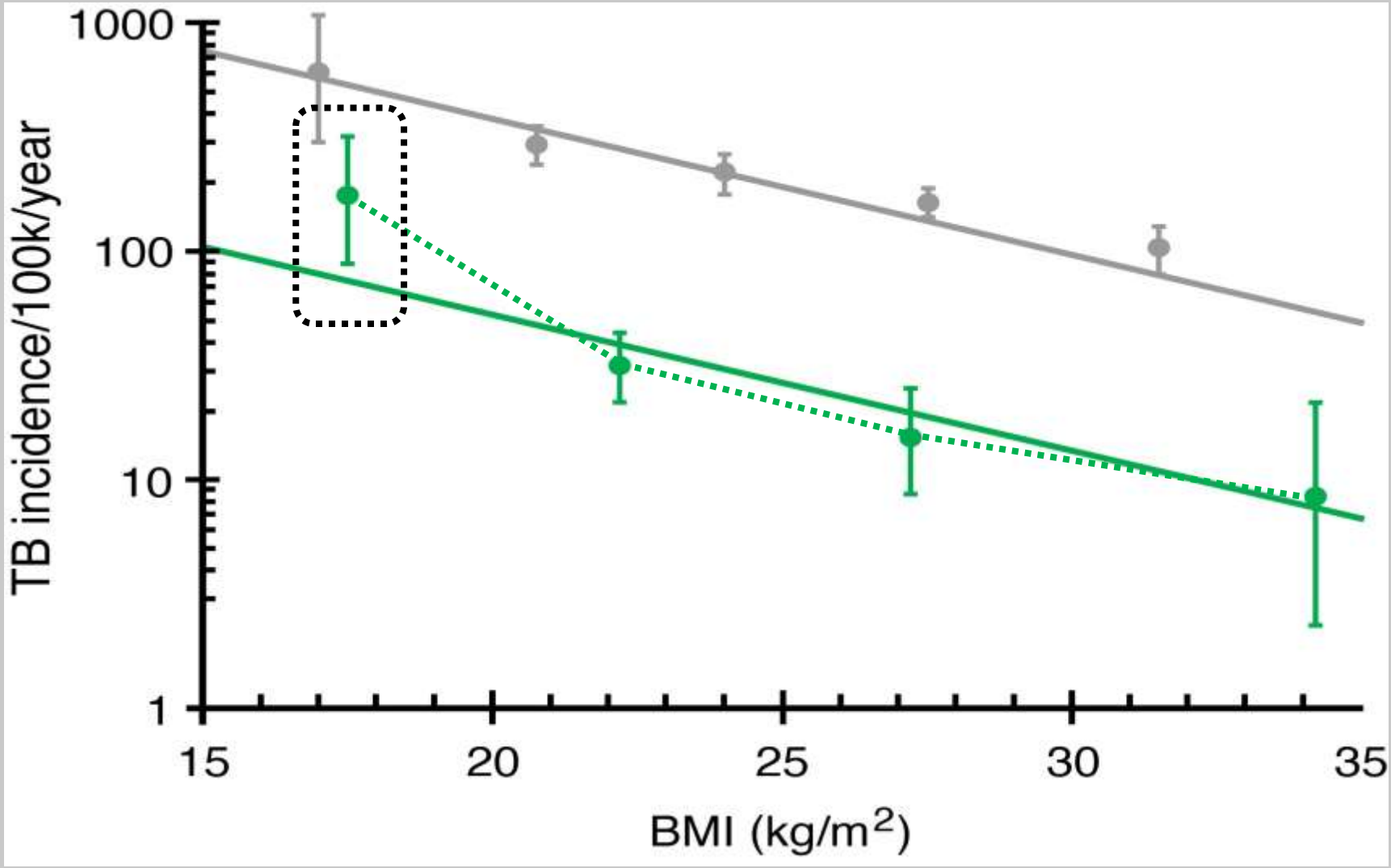
Lönnroth et al. 2010 summarized 6 studies

Palmer 1957	USA	1949 to 1951	68 754 white, male Navy recruits, 17-21y
Edwards 1971	USA	1958 to 1969	823 199 white male Navy recruits, 17-21y
Tverdal 1986	Norway	1963-75 to 1982	Nationally representative sample of 1 7171 695 Norwegians, >14y (compulsory MMR)
Cegielski 2012	USA	1971-75 to 1992	Nationally representative sample of 14 407 adults aged >24y in the USA (NHANES)
Hemilä 1999	Finland	1985 to 1993	26 975 male smokers, 50-69y, in RCT of vit. E
Leung 2007	Hong Kong	2000 to 2005	42 116 elderly (65y+) in national Elderly Health Service

Reasons for this updated meta-analysis

1. No studies included HIV infection, no children
2. All six studies in high income countries
3. Three studies only men (US Navy recruits, Finnish smokers)
4. Only two population-based representative samples (USA, Norway)
5. One study pop-based, but only elderly Chinese (Great Famine, 1959-1961)
6. Three did not control for confounding
7. *Only 2 studies had data for BMI<18.5; these 2 differed 10x in incidence rates (USA adults, Hong Kong elderly) → evidence in BMI <18.5 sparse*

Only two studies in Lönnroth 2010 included people with BMI < 18.5 kg/m2



gray, Leung

green, Cegielski

Preview

- ✓ Review 6 studies in Lönnroth et al
- ✓ Motivation behind updated meta-analysis
- ❑ New studies of BMI and TB
- ❑ IPD meta-analysis on vitamin D that also examined BMI
- ❑ Summary of studies
- ❑ Annexes: Summary of studies in PLWH , study details, search strategy

Six new studies on low BMI and TB incidence

Ackley 2015	1885-1940	Canada First Nations	First Nations native population (~2800) of W. Canada during and after relocation to reservations f/b severe famine late 1890s, followed through 1940
Moran-Mendoza 2010	1990-2000	Canada	33 146 HH contacts of TB cases province-wide in British Columbia; median 6y f-u
Park 2022	2006-2017	Republic of Korea	2 396 434 adults covered by National Health Examination with 4 consecutive annual evaluations; avg 7.3 years f-u
Aibana 2017	2009-2012	Peru	Among 6 685 HH contacts of active TB cases in shanty towns around Lima, 704 matched controls selected for 180 cases studies of vitamins A, D, E; 1 year f-u
Cho 2022	2010-2017	R. Korea	11 135 332 adults who participated in 2010 national health screening program (national mandatory annual health insurance examination)
Jurcev-Savicevic 2013	2006-2008	Croatia	300 TB cases and 300 matched controls selected from national TB database and general practitioner database

W. Canada First Nations	1885-1940	First Nations native Canadians exposed to severe famine and forced relocation	Increased risk of rapid progression after infection	aHR=5.4 (4.4, 9.9)
Canada	1990-2000	33 146 HH contacts of TB cases province-wide in British Columbia	Clinical diagnosis of malnutrition	aHR=37 (13, 111)
Republic of Korea	2006-2017	2 396 434 adults having National Health Examination, 4 consecutive annual exams	Incidence/10^5 by years underwt. 0: 51 1: 95 4: 130	aHR 1 (ref) 2.2 (1.9,2.5) 3.3 (3.0, 3.6)
Peru	2009-2012	6 685 HH contacts of active TB in shanty towns around Lima	180 cases, 704 matched controls	aHR=4.2 (1.3, 12.9)
R. Korea	2010-2017	11 135 332 adults in National Health Screening program, 2010, and mandatory annual national health insurance exam.	BMI cIR/10^3 <16.0: 3.3 16 to <17: 2.1 17 to <18.5: 1.6 18.5 to 23: ref	aHR 2.8 (2.5, 3.1) 2.5 (2.3, 2.7) 2.0 (1.8, 2.2) 1.0 (ref)
Croatia	2006-2008	300 TB cases and 300 matched controls represent geographically ½ of Croatia	300 Cases and 300 controls	aOR=13.6 (1.2, 152)

Individual patient data meta-analysis of 7 studies of vitamin D that also reported BMI (Aibana 2019)

N=3 544 total HIV+ and HIV-		aRR (95%CL)	P
	BMI underwt	1.4 (0.9, 1.9)	0.09
	BMI overwt	0.4 (0.3, -0.6)	<0.001
n=456 who developed TB	Among HIV-neg	aRR (95%CL)	
	BMI underwt	4.0 (1.8, 8.9)	0.001
	BMI overwt	0.4 (0.3, 0.6)	<0.001

LONNROTH		Summary of ratio measures of effect		NEW EVIDENCE	
Palmer 1957	Wt >15% low (BMI<19.2)	cRR=2.5 TST+ cRR=2.7	~~5.4 (4.4, 9.2) increase in rapid progression to dz~~	~~Famine~~	~~Ackley 2015~~
Edwards 1971	Wt<10% low (BMI <19.6)	cRR=1.7 TST+: cRR=1.5	aHR=37.5 (12.6, 111.4)	Clinical dx malnutrition	Moran-Mendoza 2010
~~Tverdal 1986~~	~~BMI<21~~ ~~Male~~ ~~Female~~	~~cRR=2.3~~ ~~cRR=1.7~~	aHR=2.2 (1.9,2.5), aHR=3.3 (3.0, 3.6)	BMI<18.5 1y 4y	Park 2022
Cegielski 2012	BMI <18.5	aHR=12.4 (6.5, 27.5)	2.8 (2.5,3.1), 2.5 (2.3,2.7), 2.0 (1.8,2.0)	BMI<16 BMI 16-17 BMI 17-18.5	Cho 2022
~~Hemilä 1999~~	~~BMI<23:~~	~~aRR=0.5 (0.3,0.7)~~	aHR=4.2 (1.3,12.9)	BMI<18.5	Aibana 2017
Leung 2007	BMI<18.5:	aHR=2.1 (1.6,2.8)	aHR=4.0 (1.8, 8.9)	BMI<18.5, HIV(−),	Aibana 2019
			~~aOR=13.6 (1.2, 152)~~	~~BMI<18.5 last year~~	~~2013 Jurcev-Savicevic~~

Study	Exposure	Ratio measures	n TB	N
Cho 2022	BMI <16, 16-17, 17-18.5	aHR = 2.8, 2.5, 2.0: wtd avg 2.6	52 615	11 135 332
Park 2022	1, 2, 3, 4 yr. BMI<18.5	aHR = 2.2, 2.8, 2.7, 3.3: wtd avg 2.7	9322	2 396 434
Leung 2007	BMI<18.5	aHR = 2.1 (1.6, 2.8)	477	42 116
Aibana 2019	BMI<18.5 HIV(−),	aHR = 4.0 (1.8, 8.9)	456	3544
Edwards 1971	Wt<10% low ~BMI<19.6	cRR = 1.7 (TST+: cRR = 1.5)	383	823 199
Moran-M. 2010	Clinical dx malnutrition	aHR = 37.5 (12.6, 111.4)	228	33 146
Aibana 2017	BMI<18.5	aHR = 4.2 (1.3, 12.9)	180	6685
Palmer 1957	Wt >15% low ~BMI<19.2	cRR = 2.5 (TST+ cRR = 2.7)	109	68 754
Cegielski 2012	BMI<18.5	aHR = 12.4 (5.7, 26.9)	61	14 189

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Case-weighted average

S. Korea: 2.6; Other countries: 7.1

Random Effects Model (Saunders et al.)

IRR 4.0 (2.0, 8.2)

Undernutrition and TB incidence in people living with HIV

10 Original studies + 1 SRMA on low BMI and TB incidence in PLWH* (*IPT)

Thailand, 1996-2020	Long term cohort study of 2636 PLWH aged 18+ starting ART from 1996 to 2020; median 7.6 y f-u	aHR=8.2 (2.4, 27.7)
Tanzania, 2001-08	979 HIV+ adults >18y placebo recipients in placebo-controlled randomized TB vaccine trial; mean 3.2 y f-u	per 5 kg/m2 BL BMI: aHR=1.4 (1.1,1.7) Delta BMI: aHR=3.2 (2.0,5.5) BMI < 17: aHR=3.7 (1.2, 12.)
Haiti, 2005-08	773 HIV+ adults, CD4<350, free of TB, screened with TST, followed by IPT; 61 TB cases , 251 controls	cRR*=2.0 (* calc from pub)
South Africa 2003-08	Prospective clinical cohort study of 3456 PLWH aged 18+;	aHR 1.6 (1.1, 2.3)
Cambodia 2003-10	Retrospective analysis of program and medical records for 2984 adults starting ART; 2.4 y f-u	1.6 (1.1-2.2) 2.4 (1.1–5.0)

10 Original studies + 1 SRMA on low BMI and TB incidence in PLWH* (*many with IPT)

Cambodia 2003-10	Retrospective analysis of program and medical records for 2984 adults starting ART; 2.4 y f-u	1.6 (1.1-2.2) 2.4 (1.1–5.0)
Tanzania 2011-14	Retrospective cohort study of IPT for reducing TB incidence in PLWH receiving care and treatment services, n=68 378	aHR = 1.7 (1.5–1.9) aHR = 1.8 (1.5–2.1)
Ethiopia 2013-17	633 HIV+ children<14y starting ART in HIV care at one referral hospital; median 32 months f-u	WAZ <-2: aHR: 5.2 (1.9, 14.2) WHZ <-2: aHR 2.9 (1.0, 8.0)
Uganda, Tanzania, Kenya, Nigeria, 2013-21	Longitudinal cohort study of 3171 PLHIV aged 15+	2.3 (1.3, 4.0)
Ethiopia, 2020	Retro. cohort study of 539/2168 patients receiving ART during universal test and treat program	2.4 (1.3, 4.5)
Sub-Saharan Africa 2000-22	SRMA of 43 studies of TB incidence and risk factors in PLHIV	1.8 (1.6, 2.0)

Thank you for your attention!

Details of studies presented

Palmer et al. and Edwards et al., Two US Navy Studies

Study population	Nutritional status	TB incidence/100^5/y	Ratio
N=68 754 white, male Navy recruits, age 17-21, 1949-51 followed for 4 years (IQR 3.4-5.3); N=109 TB cases	%med Wt4Ht BMI: ≥15 below ≤19.2 5-14 below 19.3-21.5 Within 4.9 21.6-23.7 ≥5% above ≥23.7	TST- TST+ All 51 264 75.1 34 214 48.5 20 110 29.7 16 70 18.9	cRR 2.5 1.5 1(ref) 0.6
823 199 white male Navy recruits aged 17-21, 1958-1969, followed for 4 years (range 2-12); 383 TB cases	%med Wt4Ht BMI: ≥10% below ≤19.6 Within 9.9% 19.7-23.9 ≥10% above >23.9	TST- TST+ ALL 59 609 170 33 407 100 17 178 48	cRR 1.7 1(ref) 0.5

Tverdal and Cegielski et al., Two Population-based Studies

Study population	Nutritional status	TB incidence /100^5/y	Ratio
1 717 695 Norwegians aged >14 years participating in compulsory mass miniature radiography, 1963-75, followed for 8-19 years; 2531 TB cases	BMI <21 21-24.9 25-28.9 >29	Male Female 294 123 129 72 72 48 41 25	Male Female 2.3 1.7 1 (ref) 0.6 0.7 0.3 0.3
14 189 NHANES-1 nationally representative sample of U.S. adults, 1971-75, followed for 17-21 years; 61 TB cases	<BMI 18.5 18.5-25 25-30 >30	Pop'n TB incidence 260 (99, 422) 25 (13, 36) 9 (2, 16) 5 (0, 10)	 12 (6, 27) 1 (ref) 0.3 (.1,.6) 0.2 (.1,.6)

Hemilä et al., male smokers in unrelated RCT
Leung et al., population-based sample of elderly

Study population	Nutrition	TB/100^5/y	Ratio
26 975 Finnish male smokers aged 50-69 in RCT of vit. E for cancer prevention, 1985-93, followed for 6.1 y (5-8y); 197 TB cases	BMI <23: 23-27: >27:	TB/100k 192 92 55	aHR 1.0 (ref) 0.5 (0.3,0.7) 0.3 (0.2,0.4)
42 116 Hong Kong Chinese elderly aged 65+ in national Elderly Health Service, 2000-05 followed for 5y (+/-0.9); 477 TB cases	Total <18.5 18.5-23 23-25 25-30 >30	226 732 291 200 148 82	 2.1 (1.6,2.8) 1.0 (ref) 0.7 (0.6,0.9) 0.6 (0.5,0.7) 0.4 (0.2,0.7)

Two new studies of BMI from Western Canada

1885-1940 W. Canada First Nations	Epidemic model of TB before/ during/ after 1890s famine coinciding with relocation to reservations; Time-varying parameters for 1) increased prob. infection, 2) increased prob. rapid progression (innate immunity vs. adaptive immunity)	Only one famine specific parameter, 5.4-fold (4.4, 9.2) increase in risk of rapid progression, best accounted for spike in TB, not risk of infection
1990-2000 Canada	British Columbia province wide population, 33 146 HH contacts (of 3485 TB cases) (excluding HIV+) followed for 6 y (0-12); 228 TB cases ($668/10^5$)	Clinical diagnosis malnutrition increased risk of TB: cHR = 28.5 (11.7, 69.3), aHR = 37.5 (12.6, 111.4)

Two new studies of BMI: HH contacts cohort in Peru, TB Case-control comparison in Croatia

Croatia 2005-2008	Case control study of 300 lab-confirmed TB patients and 300 matched controls, population representative sampling; only 2 controls and 10 cases underweight in previous year	cOR=10.0 (2.1, 47.8) aOR=13.6 (1.2,152)
Peru 2009-2012	Case-control study nested in prospective cohort of 6685 HH contacts of TB patients in Lima shanty towns followed at 2, 6, 12 mo; 180 TB cases diagnosed >90 d. after blood sample matched to 704 controls	BMI<18.5: aHR=4.2 (1.3, 12.9) Normal: 1.0 (ref) BMI>25: 0.4 (0.3, 0.6)

Two new population-bases studies from R. Korea based on national health insurance annual examination

Republic of Korea, 2006-2017	Population cohort of 2 396 434 adults with serial National Health Exams, followed for mean 7.3 years examining number of years (0-4) person was underweight; 9322 TB cases total, (8150 among 2.25m with no underweight).	Y n /10^5 aHR (CL) 0: 50.8 ref 1: 94.6 2.2 (1.9,2.5) 2: 115 2.8 (2.5, 3.2) 3: 109 2.7 (2.4, 3.2) 4: 130 3.3 (3.0, 3.6)
R. Korea, 2010-2017	Population cohort of 11 135 332 from annual National Health Insurance Examination who participated in 2010 health screening program, 52 615 TB cases over 7 years	BMI /10^3 aHR (CL) <16.0: 3.3 2.8 (2.5, 3.1) 16 to <17: 2.1 2.5 (2.3, 2.7) 17 to <18.5: 1.6 2.0 (1.8, 2.2) 18.5 to 23: 1.0 1.0 (ref)

Four original studies + 1 SRMA on low BMI and TB incidence in people with HIV

Retrospective cohort of 451 PLWH	Ethiopia	N cases 8.6 TB/100py x 1377 py	2.5 (1.3, 5.1)
Longitudinal cohort of 3171 PLHIV	Uganda, Tanzania, Kenya, Nigeria	79/13161 py (600/100k?)	2.3 (1.3, 4.0)
Long term cohort study of 2636 PLWH	Thailand	113 TB cases, 4.7/1000py (3.9, 5.6)	8.2 (2.4, 27.7)
Retrospective cohort of 539/2168 PLWH	Ethiopia	74 TB cases 4.8/100py	2.4 (1.3, 4.5)
SRMA of 43 studies	Sub-Saharan Africa	3.4/100py adults 3.8/100py children	1.8 (1.6, 2.0)

Five original studies on low BMI and TB incidence in people with HIV

979 adults, placebo recipients in TB vaccine RCT	Tanzania	92 cases x 3.2 years f-u	per 5 kg/m2 decrease (~1 category) Baseline BMI: aHR=1.4 (1.1,1.7) Yr. 1 BMI: aHR=1.7 (1.3,2.4) Change BMI: aHR=3.2 (2.0,5.5) BMI < 17 All subjects: aHR=3.7 (1.2, 12.0) TST-neg: aHR=6.1 (1.5, 25.4)
633 HIV+ children	Ethiopia	67 incident TB cases, 32 mo f-u; 6/100 p-y before ART, 2.3/100 p-y while on ART	WAZ <-2: aHR: 5.2 (1.9, 14.2) WHZ <-2: aHR 2.9 (1.0, 8.0)
Retrospective cohort of 68 378 PLWH in care and treatment	Tanzania	3124 TB cases in 114 926 py fu = 2.7/100py (2.6, 2.8)	aHR = 1.7 (1.5–1.9) aHR = 1.8 (1.5–2.1)
Retrospective analysis of 2984 adults starting ART	Cambodia	313 (10.5%) = 3.9/100py 101/179 74/134	1.6 (1.1-2.2) 2.4 (1.1–5.0)
Prospective clinical cohort study of 3456 PLWH	South Africa	226 incident cases = 4.5/100py BMI<18.5: 7.3/100 18.5-25: 6.0/100	aHR 1.6 (1.1, 2.3)

Two new studies of low BMI in PLHIV in Tanzania

2001-2008 Tanzania	979 Placebo recipients in "Dar-Dar" randomized controlled TB vaccine trial, HIV+ adults 18+ y.o. followed for 3.2 years; 92 incident TB cases total	<u>Effect per 5 kg/m2 decrease (~1 category)</u> • Baseline BMI: aHR=1.4 (1.1,1.7) • Yr. 1 BMI: aHR=1.7 (1.3,2.4) • Change BMI: aHR=3.2 (2.0,5.5) <u>BMI < 17</u> • All subjects: aHR=3.7 (1.2, 12.0) • TST-neg: aHR=6.1 (1.5, 25.4)
Tanzania 2011-2014	Retrospective analysis of 68 378 PLWH receiving care and treatment services in DSM followed for 3.4 y; 3124 TB cases in 114 926 py fu =	Incidence rate: 2.7/100py (2.6,2.8) Two aHR reported for BMI<18.5: 1.7 (1.5, 1.9) and 1.8 (1.5-2.1)

Three new studies of low BMI in PLHIV from Ethiopia

Ethiopia 11/2020	Retrospective cohort study of a SRS of 539 adults among 2168 PLWH receiving ART after universal test and treat program 0.5 to 56.6 mos f-u; 74 TB cases	Incidence rate: = 4.8/100py aHR 2.4 (1.3, 4.5)
Ethiopia 2010-2015 Ahmed	Retrospective cohort of 451 adults PLWH newly enrolled in HIV care clinic; 118 TB cases in 1377 py fu	Incidence 8.6/100 py aRR 2.5 (1.3, 5.1)
2013-2017 Ethiopia	Institution-based, retrospective record review of 633 HIV+ children starting chronic ART (42% IPT) followed for median 32 mo.; 67 incident TB cases overall	Incidence: 6/100 p-y before ART, 2.3/100 p-y while on ART • WAZ <-2: aHR: 5.2 (1.9, 14.2) • WHZ <-2: aHR 2.9 (1.0, 8.0)

Two new studies of low BMI in PLHIV from SE Asia

Thailand 1996-2020	Secondary analysis of HIVNET 006 Study cohort, 2636 PLWH aged ≥ 18 years who started ART 1996-2020; a prospective, clinic-based cohort that has enrolled adults living with HIV aged ≥ 18 years since 1996; Clinicaltrials.gov NCT00411983. 2636 PLWH x 24 229 py fu, med. 7.6 y (1.9, 15.7); 113 TB cases, increasing linearly from 0.7% at 1 year to 4.3% at 7 years	cIR=4.7/1000py (3.9, 5.6) For BMI<18.5 aSHR=8.2 (2.4, 27.7, p=0.001)
Cambodia 2003-2010	Retrospective analysis of 2984 PLWH adults starting ART fu for 2.4 yrs median based on programmatic data and medical records; 313 total TB cases = 3.9/100py, early incident TB: 179; late incident TB: 134	Early: 1.6 (1.1, 2.2) Late: 2.4 (1.1, 5.0)

Two new multinational studies of low BMI in PLHIV

Uganda, Tanzania, Kenya, Nigeria 2013-2021	Long running longitudinal "AFRICOS" cohort study of 3171 PLWH age 15+ fu for 3.0y (1.4-4.5); 79 TB cases in 13 161 py fu;	Incidence 600/100k aHR 2.3 (1.3, 4.1)
SRMA Studies published 2000-2022	SRMA of TB incidence and risk factors in PLHV in sub-Saharan Africa: 43 heterogeneous studies with N=212 to 527,000; TB cases from 15 to 22,071	cIR: 3.5/100py (2.9, 4.2) (range 0.2 to 8.8/100py) aHR: 1.8 (1.6, 2.0) (with no sig. heterogeneity)

Study of vitamin A that reported BMI

Case-cohort studies nested in RCTs of ART in HIV+ adults

Podell, 2022 **Haiti 2005-08**	**773 HIV+ adults, CD4<350, free of TB, screened with TST, followed by IPT;** **61 TB cases** **251 controls**	61 TB Cases Uwt: 15/61 (25.0) Norm: 35/61 (58.3) Owt: 10/61 (16.7) Non-cases Uwt: 32/251 (12.8) Norm: 182/251 (72.5) Owt 37/251 (14.7)	Uwt : RR*=2.0 Owt : RR*=0.9 *Crude RR computed from reported frequencies

Micronutrient studies that reported mean BMI

Getz HR 1951	Philadelphia, 1942-1949	1100 men, 83% Black, in prospective cohort study of multiple micro-nutrients	No difference in "percent of standard weight" between those who did vs did not develop TB
Soh AZ, 2017	Singapore, 1993-2014	62 257 Chinese adults 1186 incident TB cases	BMI Mean : Developed TB 22.3 (+/-3.5) Did not: 23.2 (+/-3.2) p<0.01
Tenforde, 2017	9 Countries, 2005-07	1571 HIV+ adults, CD4<300 subjects in "PEARLS" trial, ACTG #A5175	BMI Mean Developed TB: 21.6 (19.5, 22.9) No TB: 22.3 20.1, 25.1). Dif: 0.7 kg/m2, p=0.02