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How many of persistent coughers have pulmonary tuberculosis? Population-based cohort study in Ethiopia

Abiot Bezabeh Banti,[1,2] Daniel Gemechu Datiko,[3] Sven Gudmund Hinderaker,[2] Einar Heldal,[4] Mesay Hailu Dangisso,[5] Gebeyehu Assefa Mitiku ,[6] Richard Aubrey White,[7] Brita Askeland Winje [4,8]

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For numbered affiliations see end of article.

Correspondence to
Dr Brita Askeland Winje; brita.winje@fhi.no

ABSTRACT

Objective Many individuals with persistent cough and smear microscopy-negative sputum test for tuberculosis (TB) remain at risk of developing the disease. This study estimates the incidence of pulmonary TB (PTB) among initially smear-negative persistent coughers and its risk factors.

Design A prospective population-based follow-up study.

Setting Health extension workers visited all households in Dale *woreda* three times at 4-month intervals in 2016–2017 to identify individuals with symptoms compatible with TB (presumptive TB) using pretested and semistructured questionnaires.

Participants We followed 3484 presumptive TB cases (≥15 years) with an initial smear-negative TB (PTB) test.

Outcome measures Bacteriologically confirmed PTB (PTB b+) and clinically diagnosed PTB (PTB c+).

Results 3484 persons with initially smear-negative presumptive PTB were followed for 2155 person-years (median 0.8 years); 90 individuals had PTB b+ and 90 had PTB c+. The incidence rates for PTB b+ and PTB c+ were both 4176 (95% CI 3378 to 5109) per 100 000 person-years. We used penalised (lasso) and non-penalised proportional hazards Cox regression models containing all exposures and outcomes to explore associations between exposures and outcomes. In lasso regression, the risk of development of PTB b+ was 63% (HR 0.37) lower for people aged 35–64 years and 77% (HR 0.23) lower for those aged ≥65 years compared with 15–34 year-olds. Men had a 62% (HR 1.62) greater risk of PTB b+ development than women. The risk of PTB c+ was 39% (HR 0.61) lower for people aged 35–54 years than for those aged 15–34 years. Men had a 56% (HR 1.56) greater risk of PTB c+ development than women.

Conclusions PTB incidence rate among persistent coughers was high, especially among men and young adults, the latter signifying sustained transmission. Awareness about this among healthcare workers may improve identification of more new TB cases.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study was population based with a large sample size.
⇒ By embedding the study in the health system, community health workers who knew the area well were involved in identifying individuals with presumptive tuberculosis (TB) for further follow-up.
⇒ A previous smaller study conducted in the same area made it possible to explore changes over time.
⇒ Acid-fast bacilli smear microscopy was used as the principal test as this is used routinely by the TB programme in rural areas and has a very high specificity, but the sensitivity is relatively low.
⇒ We used HIV testing within the last year as a proxy for infection since information on HIV status was not available.

BACKGROUND

Sub-Saharan Africa is the region with the highest estimated tuberculosis (TB) incidence rate worldwide (226/100 000 population in 2020), and almost one-third of cases in Africa involve coinfection with HIV.[1] Ethiopia has a high burden of TB and TB/HIV coinfection, and TB ranks number 4 among causes of death in the country. Still, the estimated incidence rate of TB in Ethiopia has decreased slowly since 2007.[2 3] Over the last decades, the strategy for TB control (directly observed treatment, short course) has been implemented in the country, with varying degrees of success. The population appreciates active case finding in the communities,[4] and this expansion of care has improved case notification.[5] Approximately 10% of individuals with persistent cough in Ethiopia show bacteriological evidence of TB, but even those who test negative still may have TB.[6 7] In this large high-risk group for TB, the symptoms of the disease may be non-specific. One study showed that half of the symptomatic infectious TB cases in Ethiopia were undiagnosed in communities and concluded that more intensified ways of case finding were needed.[8] Other factors contributing to underdiagnoses are the low sensitivity of smear microscopy[9 10] and the population not seeking healthcare when they should.[11] Undiagnosed TB leads

to increased morbidity and mortality, economic hardship and sustained transmission.

Individuals with positive smear results are treated with a standard TB regimen. National guidelines recommend that persistent coughers with two negative sputum smears return for re-examination if their symptoms persist for >14 days. At re-examination, the patient may prove to not have TB, have TB in the sputum or may be diagnosed clinically, the latter two followed by TB treatment.[12] The risk of TB among persistent coughers was investigated in a study in parts of the same *woreda* 5 years earlier and in a smaller sample.[13]

The number of individuals with smear-negative presumptive TB needing follow-up visits is high and the mechanisms for follow-up are currently weak.[12 14 15] Leaving this high-risk group behind is not acceptable practice and assessment of the implications for the TB control programme has not been done. Therefore, our objectives were to: (1) estimate the incidence rate of TB among persistent coughers; and (2) assess potential determinants of TB.

METHODS

Design and setting

This study uses data from a population-based prospective cohort study conducted between October 2016 and November 2017 in Dale.[16] The population includes 3746 persons who were identified with presumptive TB based on symptoms from the household screening rounds. Among them, 262 (7%) had TB disease at enrolment, leaving 3484 persons for follow-up in the current study. Dale is located in the previous Sidama Zone, current Sidama Region, of Ethiopia, and is a densely populated agrarian community with an estimated total population of 267 000 individuals living in 36 rural *kebeles* (the smallest administrative units). The study area has 10 health centres, 2 clinics (which provide healthcare comparable to that provided at the health centres) and 36 health posts (which provide drugs under direct observed treatment short-course (DOTS) services at each *kebele*). Microscopy, but not GeneXpert nor X-ray examination, is available at the health centres. Health extension workers (HEWs) and community health workers are the main health service providers at the community level. The primary test for pulmonary TB (PTB) diagnosis is sputum smear microscopy.[17] The only GeneXpert equipment in the area is located outside of Dale in the town administration of Yirgalem.[18 19] We used the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines (online supplemental file S1).[20]

Patient and public involvement

No patients were involved in setting the research question or the outcomes, the conduct, interpretation, writing or dissemination of the results. The study was conducted in close collaboration with the *woreda* TB and leprosy programme in Dale. They were informed about the study in advance and were actively involved throughout the design and implementation phases and in dissemination of the results. The project team organised consultative meetings with participants from regional, zonal and *woreda*-level offices, non-governmental organisations and religious organisations throughout the full study period. Village women were included as representatives for the population in Dale.

Data collection and participants

Data collectors were trained for 2 days with a local and experienced project supervisor supporting the study implementation. HEWs systematically visited every household in Dale in three consecutive rounds (October 2016 to January 2017, February to May 2017 and June to September 2017) to sensitise household members to TB and ask them about the presence of symptoms compatible with TB. A symptom-screening questionnaire (online supplemental file S2) was used to identify individuals with presumptive PTB defined as cough for≥14 days, with or without related symptoms such as fever, haemoptysis, night sweats, poor appetite, weight loss, difficulty in breathing and chest pain. These individuals were referred to local services at public health posts for sputum (expectorate) collection and follow-up.

A persistent cougher was defined as a person with presumptive TB who were initially negative on sputum smear microscopy (ie, negative on the first test and any other test taken within 30 days apart). The study population included persistent coughers aged 15 years or older. The observation time was measured from the date of enrolment to the date of treatment initiation or end of study (November 2017).

Clinical samples and diagnosis

Each participant provided two spot sputum samples at the health post, which were sent to the health centre for smear microscopy. Sputum samples from smear-positive cases and those from smear-negative cases with symptom persistence after 2–4 weeks of follow-up with antibiotic treatment were sent to Yirgalem Hospital for GeneXpert-based test. Smear and/or GeneXpert-positive samples were sent to Armauer Hansen Research Institute in Addis Ababa for culture. As part of the study, quality assurance of smear microscopy results was done through rechecking of 50% random samples at the regional external quality assurance site.

Study variables

Sociodemographic, economic and clinical risk factors served as the exposure variables. We included catchment area and marital status as exposure variables in the models, as they serve as indicators of non-random differences in access to healthcare facilities and diagnosis in this setting. The outcome was a case of PTB: bacteriologically confirmed (PTB b+), clinically diagnosed (PTB c+) or both combined. PTB b+ was defined as any TB diagnosed based on smear microscopy, culture or GeneXpert

laboratory results. Clinical PTB (PTB c+) was defined by a clinical decision to start TB treatment in those with persistent cough, usually supported by radiological findings and evidence from other tests according to the National tuberculosis and leprosy (NTLP) guidelines. All-type PTB was the combination of PTB b+ and PTB c+.

Statistical analyses

Data were entered into Excel database and the quality was assessed by frequency distributions, cross-tabulations and by duplicate entry of a random sample constituting 10% of the data set. The difference between the first and second data entries was 0.1%; errors were not systematic and were corrected before further analyses with OpenEpi[21] and Stata V.14 software.[22] The incidence rate of TB was calculated by dividing the number of PTB cases by time of observation which is the number of person-years (PY). Basic descriptive analysis included median, range, mean and SD.

The R statistical software was used for regression analyses and modelling.[23] We ran separate Cox proportional hazards regression models for each exposure and exposure group, and constructed a fully adjusted model. This approach allowed us to explore confounding variables by comparing crude HR and adjusted HR (aHR) per exposure group and overall aHR; all estimated with 95% CIs. Associations were deemed significant when p values were <0.05.

For the main analyses, we ran complete-case multivariable Cox proportional hazards lasso (penalised) regression models containing all exposures for PTB, PTB b+ and PTB c+, with 1000 cross-validations. Lasso regression involves automated variable selection and yields penalised HRs; it gives no CIs nor p values (online supplemental file S3); HRs that differed from 1 were considered to be significant. It is the preferred method when adjustment for many exposure variables is required and the number of cases is limited.

RESULTS

Description of the study population

We screened 45 384 households with 136 181 adults in Dale *woreda* and identified 3746 individuals with presumptive PTB during the study period. Of them, 262 individuals had TB on initial examination and were excluded from follow-up. The remaining 3484 individuals (58% female) met the inclusion criteria for the current study of persistent coughers and were thus included for further analysis. The mean age of the study subjects was 42.7 (SD 17.4) years for men and 40.0 (SD 14.6) years for women. Seventeen presumptive PTB cases were diagnosed as extra-PTB and were excluded from further analysis. The total observation time for the participants was 786 581 person-days/2155 PY, and the median number of days under observation for participants was 301 days/0.8 years.

Incidence rates of PTB

There were 180 individuals diagnosed with PTB. PTB b+ was detected in 90 patients; 40 of them were smear and GeneXpert positive, 13 were only smear positive, 34 were only GeneXpert positive and 3 were only culture positive. There were 90 individuals diagnosed with PTB c+; GeneXpert was negative in 71 cases, invalid in 1 case and 18 were not offered this test. None of these were cultured. Chest X-rays were taken of 142 persistent coughers who could not produce sputum and/or required further investigation; 86 had findings suggestive of TB, 55 had no abnormal findings and 1 yielded a non-specific result. Only four cases did not have an X-ray as part of the PTB c+ diagnosis. The incidence rates of PTB b+ and PTB c+ were both 4176 (95% CI 3378 to 5109) per 100 000 PY. The overall incidence rate of PTB among persistent coughers was 8353 (95% CI 7197 to 9642) per 100 000 PY.

PTB risk factors

The risks of developing PTB b+ and PTB c+ among individuals with persistent cough are presented in tables 1 and 2, respectively. All-type PTB is presented in online supplemental table S1. The risks of PTB b+ and PTB c+ differed according to age (crude and adjusted p=0.001) (tables 1 and 2). The risk of developing PTB b+ and PTB c+ was significantly lower among individuals aged 35–64 years (PTB b+: lasso HR 0.37; PTB c+: lasso HR 0.61). For PTB b+, this risk was also lower among individuals aged ≥65 years (lasso HR 0.23). Men had had significantly higher risk of developing PTB b+ compared with women (lasso HR 1.62) and PTB c+ (lasso HR 1.56). Four out of nine catchment areas had significantly higher risk of PTB b+ than the reference. Increasing years of education were significantly associated with decreasing risk of developing PTB b+ (lasso HR 0.85) and PTB c+ (lasso HR 0.79, per year). Increasing middle-upper arm circumference (MUAC) was significantly associated with decreasing risk of PTB (per centimetre increase in MUAC; PTB b+: lasso HR 0.85; PTB c+: lasso HR 0.81).

Furthermore, individuals living in houses with separate kitchens had lower risk of developing PTB (PTB b+: lasso 0.85; PTB c+: lasso HR 0.46). HIV testing in the past year was associated with development of PTB (PTB b+: lasso HR 1.51; PTB c+: lasso HR 1.23). Individuals living with persistent coughers had lower risk of developing PTB c+ (lasso HR 0.43), but not PTB b+.

DISCUSSION

This study revealed a high incidence rate of PTB among persistent coughers with negative initial smear microscopy results, which was eight PTB cases per 100 PY of observation. Young adults, men, individuals with little education and those with low MUAC had increased risk of developing PTB. These results were consistent across crude, adjusted and penalised analyses for PTB b+ and PTB c+. The TB control programme should consider systematic follow-up of persistent coughers as a strategy to improve case finding.

Strengths of this study include the large sample and data collection via systematic and repeated population-based

Table 1 Risk factors for bacteriologically confirmed pulmonary tuberculosis in Dale, Ethiopia, 2016–2017

Covariates		n=3377	TB=90	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Lasso HR
Sociodemographic data								
Age group (years)		3377	90		0.001*		0.001*	
15–34		1180	60	1		1		
35–64		1902	29	0.29 (0.19 to 0.46)	0.001	0.24 (0.14 to 0.39)	0.001	0.37
65 and more		295	1	0.06 (0.01 to 0.45)	0.006	0.04 (0.01 to 0.33)	0.002	0.23
Catchment area		3377	90		0.052*		0.046*	
S Mesenkala		397	10	1		1		
Magara		215	7	1.37 (0.52 to 3.60)	0.523	1.93 (0.70 to 5.32)	0.203	–
Hida Kaliti		73	5	2.66 (0.91 to 7.79)	0.074	4.09 (1.27 to 13.1)	0.018	1.71
Bera Tadicho		423	12	1.17 (0.50 to 2.70)	0.72	3.01 (1.24 to 7.30)	0.015	1.19
Goida		254	5	0.83 (0.28 to 2.43)	0.737	1.77 (0.58 to 5.37)	0.316	–
Boa Badagalo		654	14	0.88 (0.39 to 1.99)	0.767	1.40 (0.59 to 3.32)	0.447	–
Dagyia		380	5	0.58 (0.20 to 1.69)	0.315	1.48 (0.48 to 4.52)	0.496	–
Gidamo		201	11	2.11 (0.90 to 4.97)	0.087	5.90 (2.34 to 14.8)	0.001	2.37
Moto		451	7	0.63 (0.24 to 1.65)	0.345	1.07 (0.39 to 2.90)	0.897	–
Semen Kege		329	14	1.84 (0.82 to 4.15)	0.14	3.88 (1.60 to 9.42)	0.003	1.67
Occupation		3377	90		0.283*		0.684*	
Farmer		2252	62	1		1		
Housewife		865	17	0.75 (0.44 to 1.28)	0.295	0.99 (0.54 to 1.80)	0.964	–
Merchant		68	1	0.53 (0.07 to 3.82)	0.528	0.43 (0.06 to 3.20)	0.408	–
Student		159	9	2.08 (1.04 to 4.19)	0.039	1.82 (0.81 to 4.07)	0.146	1.17
GO		15	1	2.34 (0.32 to 16.8)	0.4	1.97 (0.26 to 15.1)	0.516	–
Daily labourer		10	–	–	0.995	–	0.998	–
Other		8	–	–	0.995	–	0.998	–
Male gender		1390	50	1.81 (1.19 to 2.74)	0.005	2.31 (1.43 to 3.72)	0.001	1.62
Marital status—not married†		944	27	1.50 (0.94 to 2.39)	0.09	0.77 (0.43 to 1.36)	0.365	–
Number in household		3377	90	1.11 (0.95 to 1.29)	0.194	1.11 (0.94 to 1.31)	0.217	1.03
Years of education		3005	60	0.86 (0.80 to 0.92)	0.001	0.78 (0.72 to 0.85)	0.001	0.85
Clinical information								
MUAC (cm)		3346	90	0.83 (0.76 to 0.90)	0.001	0.80 (0.72 to 0.88)	0.001	0.85
BMI <18.5 kg/m^2‡	No	1362	20	1		1		
	Yes	2002	61	1.48 (0.95 to 2.30)	0.083	1.27 (0.80 to 2.02)	0.312	–
Risk factors for TB								
Previous TB	No	2851	73		1			
	Yes	524	17	1.17 (0.69 to 1.98)	0.563	1.38 (0.73 to 2.60)	0.32	–
TB history in the household (5 years)	No	2883	76		1			
	Yes	492	14	1.03 (0.58 to 1.82)	0.924	1.26 (0.61 to 2.59)	0.534	–
Lived with a persistent cougher	No	2443	70	1		1		
	Yes	934	20	1.17 (0.69 to 1.98)	0.563	0.57 (0.31 to 1.05)	0.07	0.88
HIV test in the past year	No	2682	63	1				
	Yes	694	27	1.42 (1.02 to 1.97)	0.037	2.18 (1.35 to 3.53)	0.002	1.51
Ever alcohol drinker§	No	3192	86	1		1		
	Yes	185	4	0.77 (0.28 to 2.09)	0.602	0.63 (0.18 to 2.15)	0.457	0.96
Ever chewed chat¶	No	3166	86	1		1		
	Yes	211	4	0.67 (0.33 to 1.36)	0.263	0.62 (0.15 to 2.66)	0.524	0.93

Continued

Table 1 Continued

Covariates		n=3377	TB=90	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Lasso HR
Ever smoker**	No	3251	87	1		1		
	Yes	126	3	0.72 (0.29 to 1.74)	0.461	1.13 (0.21 to 6.06)	0.889	–
Smoker currently in the household	No	3132	86	1		1		
	Yes	243	4	0.60 (0.22 to 1.62)	0.311	0.58 (0.16 to 2.09)	0.408	0.87
Smoker previously in the household	No	3082	82	1		1		
	Yes	294	8	1.02 (0.49 to 2.11)	0.954	1.03 (0.41 to 2.59)	0.942	–
Economic indicators								
Rooms in house (n)		3377	90	0.84 (0.65 to 1.09)	0.185	0.99 (0.73 to 1.33)	0.924	
Light source, electricity	No	2770	74	1		1		
	Yes	607	16	1.00 (0.58 to 1.72)	1	1.68 (0.92 to 3.06)	0.093	1.06
Fuel for cooking, electricity††	No	3350	90	1		1		
	Yes	27	0	–	0.995	–	0.997	
Separate kitchen	No	2643	80	1		1		
	Yes	734	10	0.43 (0.23 to 0.84)	0.013	0.38 (0.15 to 0.95)	0.038	0.85
Cooking room ventilation	No	2996	10	1		1		
	Yes	381	10	0.94 (0.48 to 1.81)	0.843	3.37 (1.41 to 8.03)	0.006	–
Heating in house	No	3287	89	1		1		
	Yes	90	1	0.43 (0.06 to 3.07)	0.398	0.26 (0.03 to 2.18)	0.213	0.86
Bank account	No	3245	88	1		1		
	Yes	130	1	0.27 (0.04 to 1.91)	0.188	0.48 (0.06 to 3.93)	0.495	0.92
Land agriculture	No	409	12	1		1		
	Yes	2968	78	0.87 (0.47 to 1.60)	0.658	1.27 (0.65 to 2.47)	0.482	–
Mobile phone	No	608	16					
	Yes	2769	74	0.93 (0.54 to 1.59)	0.777	0.72 (0.40 to 1.32)	0.291	–
TV	No	3309	89	1		1		
	Yes	68	1	0.55 (0.08 to 3.93)	0.549	1.84 (0.23 to 15.0)	0.568	–
Radio	No	2899	79	1		1		
	Yes	478	11	0.79 (0.42 to 1.49)	0.473	1.20 (0.57 to 2.52)	0.636	–
Refrigerator	No	3345	90	1		1		
	Yes	32	0	–	0.994	–	0.997	–
Walls—wood with other‡‡	No	1760	54	1		1		
	Yes	1617	36	0.70 (0.46 to 1.07)	0.102	0.93 (0.57 to 1.51)	0.758	
Roof—corrugated iron§§	No	2175	71	1		1		
	Yes	1202	19	0.47 (0.28 to 0.78)	0.003	0.53 (0.28 to 1.01)	0.054	0.69

*P value for the variable as a whole for variables with more than one value.
†Single, divorced, widowed or unknown marital status versus married (reference).
‡BMI <18.5 kg/m^2 versus BMI ≥18.5 kg/m^2 (reference).
§Ever alcohol drinker is a person who drinks alcoholic beverages to a notable level at present or in the past versus not.
¶Ever chewed chat is a person who chews chat at present or in the past versus not.
**Ever smoker is a person who smokes cigarette at present or in the past versus not.
††Use of electricity for cooking versus use of kerosene, charcoal, wood, cow dung or agricultural by-products, or no cooking in household (reference).
‡‡House walls made of brick, cement or wood with mud versus house with walls of wood only (reference).
§§Corrugated iron sheet roof versus thatched, leaf or unspecified roof (reference).
BMI, body mass index; GO, government employee; MUAC, middle-upper arm circumference; TB, tuberculosis; TV, television.

symptom screening during home visits. The bacteriological examinations were done according to the routines of TB programme with important elaboration in sputum examination (GeneXpert and culture) and quality assurance of tests. Furthermore, incidence rates were also estimated for clinically diagnosed TB cases, which is a challenge for clinicians. HEWs and community health workers were involved in the study at the grass-roots level throughout its implementation and referred symptomatic individuals immediately for further examination.

Table 2 Risk factors for clinically diagnosed pulmonary tuberculosis in Dale, Ethiopia, 2016–2017

Covariates		n=3377	TB=90	Crude HR (95% CI)		Adjusted HR (95% CI)		Lasso HR
Sociodemographic data								
Age group (years)		3377	90		0.001*		0.001*	
15–34		1168	48	1		1		
35–64		1909	36	0.45 (0.29 to 0.70)	0.001	0.46 (0.28 to 0.77)	0.003	0.61
65 and more		300	6	0.46 (0.20 to 1.07)	0.072	0.41 (0.16 to 1.01)	0.053	0.72
Catchment area		3377	90		0.001*		0.001*	
S Mesenkala		406	19	1		1		
Magara		213	5	0.53 (0.20 to 1.43)	0.21	0.59 (0.21 to 1.63)	0.309	0.92
Hida Kaliti		72	4	1.09 (0.37 to 3.19)	0.882	1.19 (0.36 to 3.89)	0.779	–
Bera Tadicho		430	19	0.97 (0.51 to 1.83)	0.923	2.68 (1.30 to 5.54)	0.008	1.99
Goida		260	11	0.97 (0.46 to 2.04)	0.934	1.62 (0.72 to 3.66)	0.246	1.54
Boa Badagalo		651	11	0.37 (0.18 to 0.79)	0.009	0.60 (0.27 to 1.30)	0.193	0.87
Dagyia		375	0	–	0.995	–	0.995	0.44
Gidamo		190	0	–	0.996	–	0.997	0.56
Moto		458	14	0.67 (0.33 to 1.33)	0.25	1.04 (0.50 to 2.19)	0.914	–
Semen Kege		322	7	0.51 (0.22 to 1.22)	0.13	0.86 (0.34 to 2.20)	0.753	–
Occupation		3377	90		0.362*		0.761*	
Farmer		2251	61	1		1		
Housewife		865	17	0.77 (0.45 to 1.31)	0.335	0.82 (0.44 to 1.52)	0.522	–
Merchant		69	2	1.05 (0.26 to 4.28)	0.95	0.63 (0.12 to 3.31)	0.582	–
Student		159	9	2.06 (1.02 to 4.15)	0.043	2.24 (0.99 to 5.06)	0.053	1.72
GO		15	1	2.29 (0.32 to 16.5)	0.41	2.22 (0.29 to 16.9)	0.444	–
Daily labourer		10	0	–	0.995	–	0.999	–
Other		8	0	–	0.995	–	0.999	–
Male gender		1388	48	1.66 (1.10 to 2.51)	0.016	2.01 (1.26 to 3.21)	0.003	1.56
Marital status—not married†		948	31	1.48 (0.93 to 2.36)	0.1	0.98 (0.55 to 1.76)	0.957	–
Number in household		3377	90	1.12 (0.96 to 1.30)	0.163	1.08 (0.92 to 1.28)	0.336	1.03
Years of education		3005	60	0.77 (0.71 to 0.83)	0.001	0.73 (0.67 to 0.80)	0.001	0.79
Clinical information								
MUAC (cm)		3346	90	0.79 (0.72 to 0.85)	0.001	0.78 (0.70 to 0.85)	0.001	0.81
BMI <18.5 kg/m^2‡	No	1374	28	1		1		
	Yes	2003	62	1.56 (1.00 to 2.44)	0.051	1.41 (0.88 to 2.27)	0.154	1.09
Risk factors for TB								
Previous TB	No	2855	77	1		1		
	Yes	520	13	0.84 (0.47 to 1.52)	0.568	1.20 (0.60 to 2.39)	0.612	–
TB history in the household (5 years)	No	2884	77	1		1		
	Yes	491	13	0.94 (0.52 to 1.69)	0.829	1.46 (0.70 to 3.04)	0.313	–
Lived with a persistent cougher	No	2453	80	1		1		
	Yes	924	10	0.32 (0.16 to 0.61)	0.001	0.22 (0.10 to 0.48)	0.001	0.43
HIV test in the past year	No	2687	68	1		1		
	Yes	689	22	1.24 (0.76 to 2.00)	0.387	1.61 (0.97 to 2.66)	0.063	1.23
Ever alcohol drinker§	No	3193	87	1		1		
	Yes	184	3	0.56 (0.18 to 1.78)	0.327	0.58 (0.14 to 2.47)	0.462	0.92
Ever chewed chat¶	No	3166	86	1		1		
	Yes	211	4	0.66 (0.24 to 1.80)	0.42	0.94 (0.23 to 3.80)	0.936	–
Ever smoker**	No	3252	88	1		1		
	Yes	125	2	0.57 (0.14 to 2.31)	0.43	0.50 (0.07 to 3.59)	0.494	0.87

Continued

Table 2 Continued

Covariates		n=3377	TB=90	Crude HR (95% CI)		Adjusted HR (95% CI)		Lasso HR
Smoker currently in the household	No	3133	87	1		1		
	Yes	242	3	0.44 (0.14 to 1.39)	0.163	1.01 (0.18 to 5.57)	0.991	0.93
Smoker previously in the household	No	3085	85	1		1		
	Yes	290	4	0.50 (0.18 to 1.35)	0.169	0.67 (0.16 to 2.86)	0.592	–
Economic indicator								
Rooms in house (n)		3377	90	0.85 (0.66 to 1.10)	0.222	0.94 (0.69 to 1.26)	0.663	–
Light source, electricity	No	290	4	1		1		
	Yes	3085	85	0.78 (0.44 to 1.41)	0.416	0.98 (0.50 to 1.93)	0.949	–
Fuel for cooking, electricity††	No	3350	90	1		1		
	Yes	27	0	–	0.995	–	0.999	
Separate kitchen	No	2643	80	1		1		
	Yes	734	10	0.16 (0.06 to 0.44)	0.001	0.20 (0.06 to 0.68)	0.01	0.46
Cooking room ventilation	No	3001	85	1		1		
	Yes	376	5	0.44 (0.18 to 1.08)	0.072	1.55 (0.52 to 4.63)	0.433	–
Heating in house	No	3288	90	1		1		
	Yes	89	0	–	0.994	–	0.997	0.97
Bank account	No	3245	88	1		1		
	Yes	132	2	0.53 (0.13 to 2.14)	0.369	0.93 (0.14 to 6.20)	0.941	–
Land agriculture	No	397	24	1		1		
	Yes	2956	66	0.37 (0.23 to 0.59)	0	0.51 (0.30 to 0.86)	0.012	0.55
Mobile phone	No	2771	76	1		1		
	Yes	606	14	0.78 (0.44 to 1.38)	0.391	1.23 (0.65 to 2.31)	0.524	–
TV	No	3309	89	1		1		
	Yes	68	1	0.55 (0.08 to 3.92)	0.548	0.29 (0.01 to 6.97)	0.444	–
Radio	No	2901	81	1		1		
	Yes	476	9	0.63 (0.31 to 1.25)	0.183	1.20 (0.55 to 2.61)	0.651	–
Refrigerator	No	3343	88	1		1		
	Yes	34	2	2.29 (0.56 to 9.31)	0.246	6.52 (0.95 to 44.4)	0.056	1.29
Walls—wood with other‡‡	No	1773	67	1		1		
	Yes	1604	23	0.36 (0.23 to 0.58)	0.001	0.43 (0.25 to 0.74)	0.002	0.52
Roof—corrugated iron§§	No	2176	72	1		1		
	Yes	1201	18	0.44 (0.26 to 0.73)	0.002	0.98 (0.52 to 1.85)	0.944	–

*P value for the variable as a whole for variables with more than one value.
†Single, divorced, widowed or unknown marital status versus married (reference).
‡BMI <18.5 kg/m^2 versus BMI ≥18.5 kg/m^2 (reference).
§Ever alcohol drinker is a person who drinks alcoholic beverages to a notable level at present or in the past versus not.
¶Ever chewed chat is a person who chews chat at present or in the past versus not.
**Ever smoker is a person who smokes cigarette at present or in the past versus not.
††Use of electricity for cooking versus use of kerosene, charcoal, wood, cow dung or agricultural by-products, or no cooking in household (reference).
‡‡House walls made of brick, cement or wood with mud versus house with walls of wood only (reference).
§§Corrugated iron sheet roof versus thatched, leaf or unspecified roof (reference).
BMI, body mass index; GO, government employee; MUAC, middle-upper arm circumference; TB, tuberculosis; TV, television.

This strong collaboration strengthened the quality of the field study. Since we included clear and reproducible exposures in the analyses, the results may be included in meta-analyses and further validated by other studies. The study also had some weaknesses. Information on HIV status was not available and information on HIV testing within the last year was used as a proxy for infection. As smear microscopy was used as the principal test, case numbers could have been underestimated due to the suboptimal sensitivity of this test. GeneXpert expansion to the primary healthcare level in the rural setting could improve case detection. Furthermore, symptom-based screening can miss up to half of PTB b+ cases who present with no or very few symptoms.[13 24] The repeated screening in this study might have helped to reduce the risk of missed cases.

Compared with a study conducted among persistent coughers 5 years ago (2011–2012) which covered six of the 36 kebeles included in the current study (online supplemental table S2), we found a lower incidence rate for smear-positive TB at 1502/100 000 PY compared with the previous 3912/100 000 PY.[13] The decline is similar to the overall decline in case notification in Dale (10% vs 9%) in this period. During the same period, the regional case notification increased but nationally declined slowly by 3% per year.[5] The expansion and decentralisation of the DOTS strategy to the health posts over this period may have improved service delivery. There were also methodological differences between the previous study and ours, such as participant selection, design and analysis, which restrict the comparison.

We found no other reports of estimation of incidence rates of PTB c+ among persistent coughers in the literature; thus, comparison is limited to the incidence rates of PTB b+. The proportion of PTB b+ among persistent coughers was higher than routine TB control in this study as expected. This may be partly due to more elaborate testing of risk groups; GeneXpert and culture are not routinely available in rural areas. In most low-income countries, GeneXpert testing is limited to larger centres. TB diagnosis at peripheral sites was based mainly on smear microscopy at the time of the study.[13]

Male persistent coughers had greater risks of developing PTB b+ and PTB c+ compared with their female counterparts in this study. Consistent with this finding, gender disparities in TB notification are common in many countries, with more men than women affected, and with longer delay in diagnosis for men.[25] However, a recent study showed a male to female ratio of TB cases close to 1 in a setting similar to that of Dale.[26] Furthermore, other studies have revealed more TB cases among females than among males in Ethiopia,[11 27] the reason could be better access due to community screening. Since 2010, HEWs have implemented community-based active case finding in the study area, increasing the awareness of TB in this population.[4] Thus, previous community care interventions to raise awareness of TB in the population may have contributed to the identification of persistent coughers. A previous study showed varying numbers of PTB in different locations in the study area.[28] The study conducted in the northern and southern parts of Ethiopia suggests that clustering (ie, geographical distribution) is common.[29] Variable programme performances, including reporting completeness, access to diagnosis and population density, are well-known factors contributing to clustering.[30] The national poverty line has been declining since 2004 in the country, but the reduction in rural areas where the poorest segments of the populations are concentrated has been slower. Around 67% of adults in this population group have not completed primary education.[31] In one study conducted in Ethiopia, the risk of developing TB was almost three times greater among individuals with low educational levels as compared with well-educated individuals.[32] Similarly, in our study, individuals with little education had higher rates of PTB b+ and PTB c+ in both crude and adjusted analyses. Access to a separate kitchen reduced the risks of PTB b+ and PTB c+. These findings are consistent with those of a study conducted in India, in which improved housing wall types and separate kitchens were associated with a reduced risk of TB.[33] Poorly built housing is strongly related to poverty[34] and poverty is related to the TB risk.[4] A low MUAC was associated with higher risk of developing PTB, which is no surprise as wasting is a key symptom of TB. However, undernutrition is a known factor for development of TB.[35] HIV is one of the strongest known risk factors for developing TB.[5] The prevalence of HIV in southern region was low at 0.4% among 15–49 year-olds,[36] and HIV coinfection among patients with TB in the study area is much lower than the national level at 0.7%.[37] The region of this study has the lowest prevalence of HIV in the country at 0.4%[36] among 15–49 year-olds. HIV testing was not included in the study as blood sampling was not feasible at community level at that time. Only individuals identified with TB were tested and the remaining participants reported whether they had been HIV tested within the last year or not. We do not know the reason for HIV testing, nor the result, but still found that reporting an HIV test was associated with PTB. Living with a known patient with TB (under treatment) in the household was not associated with PTB. However, living with a persistent cougher (with no proven TB at the baseline) was associated with developing PTB c+ (but not PTB b+) compared with living without coughers in the house. Persistent cough is a non-specific indicator with various underlying aetiologies. It is prevalent among older people regardless of the TB prevalence in this age group. One study showed that almost 12% of older adults in Ethiopia had cough of >2 weeks' duration, but they had a lower risk of TB than young people.[38]

Penalised regression models reduce the variability (inconsistency) of the results but may have bias. In contrast, multivariable regression results tend to have less bias, but greater variability. We analysed both with proportional Cox regression models and lasso regression, with many adjustments the latter may give more reliable results.

CONCLUSIONS

This study showed a high incidence rate of PTB among persistent coughers in Ethiopia. The rate was highest among men and young adults suggesting sustained community transmission. Awareness among healthcare workers about the importance of follow-up of persistent coughers may improve early detection of PTB and reduce transmission in the community. HEWs and community health workers have the capacity to provide TB care where access to diagnostic services, referral, and recording and reporting are in place. Thus, through their training they may be reminded to be particularly aware of symptoms among young adults.

Author affiliations
[1]USAID Urban TB LON project, REACH Ethiopia, Addis Ababa, Ethiopia
[2]Centre for International Health, University of Bergen, Bergen, Norway
[3]USAID Eliminate TB Project, Management Sciences for Health Ethiopia, Addis Ababa, Ethiopia
[4]Department of Infection Control and Vaccine, Norwegian Institute of Public Health, Oslo, Norway
[5]School of Public Health, Hawassa University, Hawassa, Ethiopia
[6]Armauer Hansen Research Institute, Addis Ababa, Ethiopia
[7]Department of Methods Development and Analytics, Norwegian Institute of Public Health, Oslo, Norway
[8]Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway

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Contributors BAW, DGD and EH conceived the study. ABB, DGD and GAM implemented the study in the community and collected the data. ABB, DGD, BAW and EH supervised the fieldwork. ABB, BAW and RAW analysed the data and drafted the manuscript. RAW was responsible for the statistical analyses. ABB, MHD, SGH, DGD, EH, RAW and BAW finalised the write-up. All authors reviewed and approved the final version of the manuscript. BAW acts as guarantor of the publication.

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ORCID iDs
Gebeyehu Assefa Mitiku http://orcid.org/0000-0003-1308-7566
Brita Askeland Winje http://orcid.org/0000-0003-2858-7248

REFERENCES

1 World Health Organization. *Global tuberculosis report 2020*. Geneva, 2020.
2 Global burden of disease, 2015. Available: https://vizhub.healthdata.org/gdb-compare/ [Accessed 11 May 2020].
3 World Health Organization. *Global tuberculosis report*. Geneva: World Health Organization, 2018.
4 Tulloch O, Theobald S, Morishita F, *et al*. Patient and community experiences of tuberculosis diagnosis and care within a community-based intervention in Ethiopia: a qualitative study. *BMC Public Health* 2015;15:187.
5 Datiko DG, Yassin MA, Theobald SJ, *et al*. Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study. *BMJ Glob Health* 2017;2:e000390.
6 Federal Democratic Republic of Ethiopia Ministry of Health. *Tuberculosis leprosy and TB/HIV prevention and control program manual*. Addis Ababa, Ethiopia, 2016.
7 Federal Democratic Republic of Ethiopia Ministry of Health. *TB program managment training manual Module 6*. Addis Ababa, Ethiopia, 2017.
8 Hamusse S, Demissie M, Teshome D, *et al*. Prevalence and incidence of smear-positive pulmonary tuberculosis in the Hetosa district of Arsi zone, Oromia regional state of central Ethiopia. *BMC Infect Dis* 2017;17:214.
9 World Health Organization. *Toman's tuberculosis case detection, treatment, and monitoring-questions and answers*. 2nd edn. Geneva, Switherland, 2004.
10 Keflie TS, Ameni G. Microscopic examination and smear negative pulmonary tuberculosis in Ethiopia. *Pan Afr Med J* 2014;19:162.
11 Christian C, Burger C, Claassens M, *et al*. Patient predictors of health-seeking behaviour for persons coughing for more than two weeks in high-burden tuberculosis communities: the case of the Western Cape, South Africa. *BMC Health Serv Res* 2019;19:160.
12 Federal Democratic Republic of Ethiopia Ministry of Health. *National guidelines for TB, DR-TB and leprosy in Ethiopia*. Addis Ababa, Ethiopia, 2018.
13 Woldesemayat EM, Datiko DG, Lindtjørn B. Follow-up of chronic coughers improves tuberculosis case finding: results from a community-based cohort study in southern Ethiopia. *PLoS One* 2015;10:e.0116324.
14 Federal Democratic Republic of Ethiopia Ministry of Health. *National strategic plan tuberculosis and leprosy control 2013/14-2020 with updat-for 2018-2020/21*. Addis Ababa, Ethiopia, 2018.
15 Federal Democratic Republic of Ethiopia Ministry of Health. *Health sector development plan 2010-2015*. Addis Ababa, Ethiopia, 2010.
16 REACH Ethiopia. Population-based tuberculosis case finding in dale district. Available: https://www.reachet.org.et/index.php/projects/tb-niph [Accessed 09 Sep 2021].
17 Yajko DM, Nassos PS, Sanders CA, *et al*. High predictive value of the acid-fast smear for *Mycobacterium tuberculosis* despite the high prevalence of *Mycobacterium avium* complex in respiratory specimens. *Clin Infect Dis* 1994;19:334–6.
18 Ministry of Health, Federal Republic of Ethiopia. *National strategic plan for tuberculosis and leprosy control 2021 to 2026*. Addis Ababa, Ethiopia, 2021.
19 World Health Organization. *Treatment of tuberculosis: guidelines for national programmes*, 1997.
20 Von Elm E, Altman DG, Egger M. *The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies*, 2014.
21 Soe MM, Sullivan KM, Dean AG. Open source epidemiologic statistics for public health, 2013Emory University. Available: www.OpenEpi.com [Accessed 10.10.2016].
22 StataCorp LP. Stata Statistical SoftwareRelease 14. College Station, TX:. 2015.
23 R: a language and environment for statistical computing. Available: https://www.r-project.org/
24 Frascella B, Richards AS, Sossen B, *et al*. Subclinical tuberculosis disease—a review and analysis of prevalence surveys to inform

definitions, burden, associations, and screening methodology. *Clinical Infectious Diseases* 2021;73:e830–41.
25 Chikovore J, Hart G, Kumwenda M, *et al*. Tb and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. *Int J Tuberc Lung Dis* 2017;21:26–33.
26 Datiko DG, Guracha EA, Michael E, *et al*. Sub-national prevalence survey of tuberculosis in rural communities of Ethiopia. *BMC Public Health* 2019;19:295.
27 Tadesse T, Demissie M, Berhane Y, *et al*. Two-Thirds of smear-positive tuberculosis cases in the community were undiagnosed in Northwest Ethiopia: population based cross-sectional study. *PLoS One* 2011;6:e28258.
28 Dangisso MH, Datiko DG, Lindtjørn B. Spatio-temporal analysis of smear-positive tuberculosis in the Sidama zone, southern Ethiopia. *PLoS One* 2015;10:e0126369.
29 Tadesse T, Demissie M, Berhane Y, *et al*. The clustering of smear-positive tuberculosis in Dabat, Ethiopia: a population based cross sectional study. *PLoS One* 2013;8:e65022.
30 Dangisso MH, Datiko DG, Lindtjørn B. Identifying geographical heterogeneity of pulmonary tuberculosis in southern Ethiopia: a method to identify clustering for targeted interventions. *Glob Health Action* 2020;13:1785737.
31 Federal Democratic Republic of Ethiopia. *Planning and development commission, Poverty economic growth in Ethiopia*, 2018.
32 Taha M, Deribew A, Tessema F, *et al*. Risk factors of active tuberculosis in people living with HIV/AIDS in Southwest Ethiopia: a case control study. *Ethiop J Health Sci* 2011;21:131–9.
33 Singh SK, Kashyap GC, Puri P. Potential effect of household environment on prevalence of tuberculosis in India: evidence from the recent round of a cross-sectional survey. *BMC Pulm Med* 2018;18:66.
34 Cambanis A, Yassin MA, Ramsay A, *et al*. Rural poverty and delayed presentation to tuberculosis services in Ethiopia. *Trop Med Int Health* 2005;10:330–5.
35 Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004;8:286–98.
36 CSA and ICF. *Ethiopian demograpphic health survey 2016: HIV report*. Addis Ababa, Ethiopia, and Rockville, Maryland, USA: CSA and ICF, 2016.
37 Federal Democratic Republic of Ethiopia Ministry of Health. *Annual National TB program report 2017/18*. Addis Ababa, Ethiopia, 2017.
38 Kebede AH, Alebachew Z, Tsegaye F, *et al*. The first population-based national tuberculosis prevalence survey in Ethiopia, 2010-2011. *Int J Tuberc Lung Dis* 2014;18:635–9.