

Social and health factors associated with unfavourable treatment outcome in adolescents and young adults with tuberculosis in Brazil: a national retrospective cohort study

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Summary

Background Tuberculosis elimination strategies in Brazil might neglect adolescents and young adults aged 10–24 years, hampering tuberculosis control. However, little is known about factors associated with tuberculosis treatment outcomes in this underserved group. In this study, we aimed to investigate social and health factors associated with unfavourable treatment outcomes in young people with tuberculosis in Brazil.

Methods A national retrospective cohort study was done using data from Sistema de Informação de Agravos de Notificação (SINAN), the national tuberculosis registry in Brazil. People aged 10–24 years (young people) with tuberculosis registered in SINAN between Jan 1, 2015, and Dec 31, 2018, were included. Unfavourable outcomes were defined as loss to follow-up, treatment failure, and death. Favourable outcome was defined as treatment success. Multiple logistic regression models estimated the association between social and health factors and tuberculosis treatment outcomes.

Findings 67 360 young people with tuberculosis were notified to SINAN, and we included 41 870 young people in our study. 7024 (17%) of the 41 870 included individuals had unfavourable treatment outcomes. Young people who received government cash transfers were less likely to have an unfavourable outcome (adjusted odds ratio 0·83, 95% CI 0·70–0·99). Homelessness (3·03, 2·07–4·42), HIV (2·89, 2·45–3·40), and illicit drug use (2·22, 1·93–2·55) were the main factors associated with unfavourable treatment outcome.

Interpretation In this national cohort of young people with tuberculosis in Brazil, tuberculosis treatment success rates were lower than WHO End TB Strategy targets, with almost a fifth of participants experiencing unfavourable treatment outcomes. Homelessness, HIV, and illicit drug use were the main factors associated with unfavourable outcome. In Brazil, strategies are required to support this underserved group to ensure favourable tuberculosis treatment outcomes.

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Introduction

Tuberculosis is a disease of poverty, which disproportionately affects individuals who are socially and economically vulnerable.^{1–3} Before the COVID-19 pandemic, tuberculosis was the leading cause of death from a single infectious agent globally.⁴ Modelling studies have suggested that COVID-19 will probably threaten tuberculosis control programmes, particularly in low-income and middle-income settings, affecting tuberculosis prevention, case detection, and management.⁵

Before the COVID-19 pandemic, WHO estimated that less than 70% of all new tuberculosis cases were notified to surveillance systems and this proportion was likely to be even lower among young people aged 10–24 years (hereafter referred to as young people; appendix p 1).^{4,6} In 2018, the global burden of tuberculosis for young people was calculated for the first time. An estimated 1·8 million young people developed tuberculosis disease in 2018, comprising 17% of all new tuberculosis cases worldwide.⁶ Compared with children, young people are

at increased risk of tuberculosis infection, tuberculosis disease, and tuberculosis-related complications.^{7,8}

The transition from adolescence to adulthood is associated with a cumulative increase in tuberculosis incidence.⁶ Young people are more likely to develop infectious forms of tuberculosis than children under 5 years of age, independent of HIV status.^{9,10} Moreover, young people have greater potential to contribute to onward tuberculosis transmission, which not only relates to an increased likelihood of infectious pulmonary tuberculosis but also to engagement with wider social networks and attendance at educational institutions and activity in the labour market, with the highest risk of transmission between 12 and 24 years of age.^{7–9,11} However, young people are often overlooked in national tuberculosis treatment and prevention strategies, with tuberculosis treatment programmes mostly focusing on adults and prevention strategies prioritising children under 5 years.^{6,12} Even in countries with high tuberculosis burden, health-care providers might often perceive

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Research in context

Evidence before this study

We used Google Scholar, PubMed, and Embase to search for papers that were published in Portuguese and English between database inception and Jan 1, 2021, and that evaluate young people with tuberculosis in Brazil, using the terms “Tuberculosis”, “TB”, “Young People”, “Adolescents”, “Young Adults”, “Unfavourable Treatment Outcome”, “Adverse Treatment Outcome”, “Loss to Follow Up”, “Death”, “Brazil”, “High Burden Country”, “TB Incidence Rates”. The studies identified from this search were restricted either to paediatric or adolescent populations and did not include updated variables on social and health vulnerability in their analyses (deprivation of liberty, homelessness, illicit drug use, tobacco use, and government cash transfers).

Added value of this study

To our knowledge, this study is the first nationally representative analysis of the characteristics of young people (aged 10–24 years) with tuberculosis in Brazil and evaluation of the factors associated with unfavourable tuberculosis treatment outcomes in this age group. The study used population-level

clinical registry data retrieved from an updated version of the national Brazilian diseases registry (Sistema de Informação de Agravos de Notificação). The study found that tuberculosis treatment success rates were lower than WHO End TB Strategy targets with almost a fifth of participants experiencing unfavourable outcome. Homelessness, HIV, and illicit drug use were the main factors associated with unfavourable outcome. Young people who received government cash transfers were less likely to have unfavourable outcomes.

Implications of all the available evidence

This study contributes to a growing evidence base that young people with tuberculosis need greater attention in national tuberculosis control programmes, which is particularly relevant for policy makers, health-care providers, and civil society representatives. The findings emphasise the need for individualised, patient-centred tuberculosis care for young people, and indicate the potential for targeted social support and protection strategies to increase treatment success of young people with tuberculosis.

tuberculosis as a disease that seldom affects young people.¹³

Approximately nine in ten young people live in low-income and middle-income countries, many of which are also countries with high tuberculosis burden.^{13,14} Brazil, an upper-middle-income country, is among the 30 countries with the highest burden of tuberculosis globally.⁴ In Brazil, between 2015 and 2018, 67 360 (19%) of the 357 155 total tuberculosis cases were among young people.^{15,16} However, there are no specific public health policies targeting young people with tuberculosis in Brazil. Moreover, there are no nationally representative longitudinal studies evaluating the factors associated with unfavourable treatment outcomes for young people with tuberculosis in this context. Doing such research is of importance not only from a human rights perspective but also because unfavourable tuberculosis treatment outcomes for young people increases the likelihood of onward tuberculosis transmission, tuberculosis-related morbidity and mortality, and adverse socioeconomic outcomes.

Using prospective clinical registry data derived from Sistema de Informação de Agravos de Notificação (SINAN), the Brazilian national tuberculosis registry and one of the largest of its kind in the world, we sought to investigate the social and health factors associated with unfavourable treatment outcomes among young people with new tuberculosis diagnosis in Brazil.

Methods

Study design and participants

We did a national retrospective cohort study of young people with tuberculosis in Brazil, using de-identified

registry data derived from SINAN, the Brazilian national tuberculosis registry.^{16,17} Study inclusion criteria were defined as all individuals aged 10–24 years, referred to as young people, notified to SINAN with a new diagnosis of tuberculosis between Jan 1, 2015, and Dec 31, 2018. This definition of young people has been used by the United Nations Population Fund,¹⁴ and in related studies.⁶ We excluded individuals who were notified to SINAN due to tuberculosis recurrence or return following loss to follow-up, those who had a tuberculosis diagnosis at post-mortem examination, and those who had a missing notification status. We also excluded individuals who had missing treatment outcomes (still undergoing treatment), those whose outcome was recorded as transfer to other health-care centre, those whose diagnosis changed during tuberculosis treatment, or those whose outcome was recorded as drug-resistant tuberculosis. The outcomes of individuals with drug-resistant tuberculosis at time of notification were not recorded in SINAN but rather in a separate registry (Special Treatment of Tuberculosis Information System).¹⁸ Therefore, outcomes of young people with drug-resistant tuberculosis were not included in this study.

This study was done under the Declaration of Helsinki, and adheres to Brazilian, Swedish, and UK research regulations on the use of de-identified secondary data for research. SINAN is an open-access data platform, which seeks to democratise public health research in Brazil. The main supervising institution (Karolinska Institutet) waived the need for formal ethics approval given the use of de-identified, secondary level

registry data. Tuberculosis notifications to SINAN are not linked to other registries, and therefore there is minimal risk of the dataset being used to derive, ascertain, or disclose any further patient-identifiable information.¹⁸

Study context

Tuberculosis is a mandatory notifiable infectious disease in Brazil, and the Sistema Único de Saúde (SUS), Brazil's national public health-care system, provides free and accessible tuberculosis treatment at the point of care throughout Brazil in coordination with the Programa Nacional de Controle da Tuberculose (the National Tuberculosis Control Programme). However, geographical and regional disparities in tuberculosis services, care, and treatment outcomes persist, and these disparities are even observed at a macroregional level (north, northeast, centre-west, southeast, and south).¹⁹ Of concern, SUS is under increasing pressure in the context of economic and political shocks since 2016, most recently including the COVID-19 pandemic and preceding economic crises and severe austerity measures.²⁰ In conjunction with SUS, Programa Bolsa Família, the largest government social protection programme globally, strives to reduce the burden of poverty in Brazil and secondarily might reduce the risk of out-of-pocket expenditure and catastrophic health costs for Brazilians who become unwell, including those who fall ill with tuberculosis.²¹

SINAN is a decentralised system in Brazil and consists of clinical notifications for specified notifiable diseases.^{16,17} The surveillance system was first conceived in 1990 and represents one of the largest national tuberculosis registries among countries with high tuberculosis burden, providing valuable data on tuberculosis epidemiology for researchers and health professionals.

With reference to the conceptual framework from Maciel and Reis-Santos, which comprises three axes of individual, social, and institutional vulnerability,²² particular social and health variables were extracted from SINAN. These variables were: (1) individual vulnerability variables: age, sex, skin colour, tobacco use, alcohol misuse, illicit drug use, and HIV or AIDS status; (2) social vulnerability variables: extent of urbanisation, region of Brazil, educational attainment, inclusion in government cash transfers, homelessness, and deprivation of liberty; and (3) institutional vulnerability variables: chest radiography findings, baseline smear microscopy, clinical features of tuberculosis, treatment supervision, total number of contacts identified, and total number of contacts traced.

To standardise educational attainment by age, when comparing adolescents and young adults, we created a variable to ascertain whether the educational attainment of the young people was lower than expected for their age. As per related guidance, we assumed that all young people should be literate, people over 12 years of age should have completed 4th grade (>5 years of education),

all young people over 16 years of age should have completed elementary school (>9 years of education), and all young people over 19 years of age should have completed high school (>12 years of education).²³

A composite binary variable of contact tracing was generated by calculating the total number of contacts identified minus the total number of contacts traced. If this value was less than or equal to zero, contact tracing was assumed to be successfully completed (all contacts initially identified had been successfully contact traced, or additional contacts to those initially identified had been successfully contact traced).

Outcomes

The main study outcome was tuberculosis treatment outcome: a binary categorical variable of either favourable or unfavourable treatment outcome. Favourable treatment outcomes consisted of treatment completion and cure. For pulmonary tuberculosis, cure was defined as clinician-led discharge from tuberculosis care following completion of tuberculosis treatment and a minimum of two negative sputum smear tests, or completion of tuberculosis treatment in the absence of sputum smear microscopy;²¹ for extra-pulmonary tuberculosis, cure was defined as the completion of tuberculosis treatment or evidence of clinical improvement and radiological resolution.²¹ Unfavourable treatment outcome was

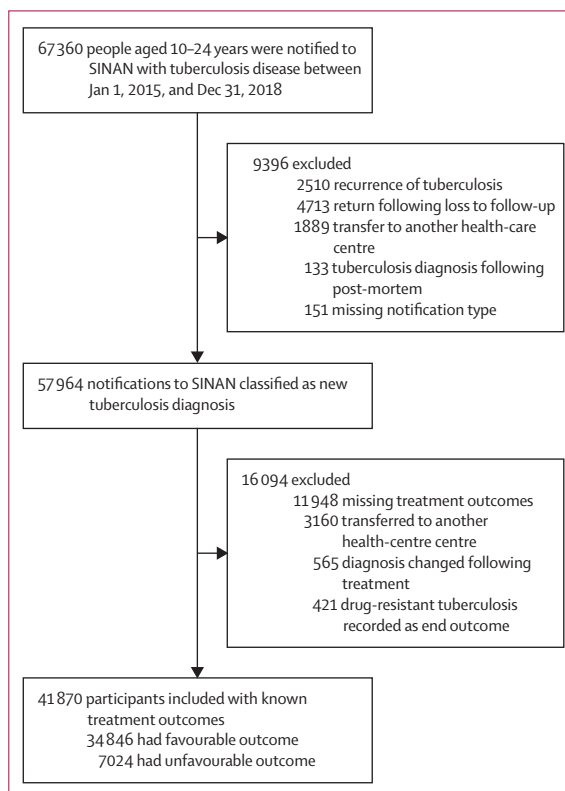


Figure 1: Participant selection

SINAN=Sistema de Informação de Agravos de Notificação.

	Young people with tuberculosis	Unfavourable treatment outcome
Age (n=41 870)		
Adolescents (aged 10–17 years)	8826 (21%)	1000 (14%)
Young adults (aged 18–24 years)	33 044 (79%)	6024 (86%)
Sex (n=41 867)		
Female	14 521 (35%)	2034 (29%)
Male	27 346 (65%)	4989 (71%)
Skin colour (n=38 762)		
White	12 666 (33%)	1725 (27%)
Black	4895 (13%)	994 (15%)
Brown	20 307 (52%)	3653 (56%)
Asian	286 (1%)	43 (1%)
Indigenous	608 (2%)	65 (1%)
Low education attainment (n=32 590)		
No	15 207 (47%)	1786 (34%)
Yes	17 383 (53%)	3404 (66%)
Tobacco use (n=39 044)		
No	33 301 (85%)	4890 (77%)
Yes	5743 (15%)	1489 (23%)
Alcohol misuse (n=39 424)		
No	36 292 (92%)	5525 (85%)
Yes	3132 (8%)	939 (15%)
Illicit drug use (n=38 889)		
No	32 913 (85%)	4502 (71%)
Yes	5976 (15%)	1871 (29%)
HIV (n=37 813)		
No	35 904 (95%)	5394 (87%)
Yes	1909 (5%)	810 (13%)
Diabetes (n=39 313)		
No	38 928 (99%)	6349 (99%)
Yes	385 (1%)	88 (1%)
Extent of urbanisation (n=28 521)		
Rural	2692 (9%)	341 (7%)
Urban	25 503 (89%)	4740 (92%)
Peri-urban	326 (1%)	55 (1%)

(Table 1 continues in next column)

defined as either (1) loss to follow-up, whereby treatment was disrupted for 30 days or more; (2) mortality during tuberculosis treatment from any cause; (3) change in tuberculosis treatment regimen; or (4) tuberculosis treatment failure, whereby sputum smear or culture was positive at 4 months or for 2 consecutive months after the 4th month of tuberculosis treatment initiation.²⁰ Final tuberculosis treatment outcomes were recorded within 9 months of initial notification to SINAN, or within 15 months for cases with central nervous system involvement.²¹

Statistical analysis

We did univariate and multiple logistic regression analyses to estimate the association between social and health factors recorded at the time of tuberculosis

	Young people with tuberculosis	Unfavourable treatment outcome
(Continued from previous column)		
Region of Brazil (n=41 870)		
Southeast	21 184 (51%)	3440 (49%)
North	5149 (12%)	900 (13%)
Northeast	9717 (23%)	1649 (23%)
South	4337 (10%)	766 (11%)
Central-west	1483 (4%)	269 (4%)
Government cash transfers (n=22 668)		
No	20 462 (90%)	3652 (92%)
Yes	2206 (10%)	321 (8%)
Homelessness (n=39 126)		
No	38 714 (99%)	6227 (96%)
Yes	412 (1%)	247 (4%)
Deprivation of liberty (n=39 415)		
No	33 142 (84%)	5754 (88%)
Yes	6273 (16%)	771 (12%)
Clinical features of tuberculosis (n=41 868)		
Extra-pulmonary tuberculosis	4745 (11%)	726 (10%)
Pulmonary tuberculosis	37 123 (89%)	6298 (90%)
Baseline smear microscopy (n=30 408)		
Negative	7239 (24%)	1124 (23%)
Positive	23 169 (76%)	3830 (77%)
Chest radiography findings (n=27 956)		
Normal	1679 (6%)	240 (5%)
Abnormal	26 277 (94%)	4610 (95%)
Data are n (%).		

Table 1: Social and health characteristics of participants (excluding missing data)

notification and unfavourable treatment outcomes.²² The association was estimated using crude and adjusted odds ratios (OR), 95% CIs, and Wald test p values. p values of less than 0.05 were considered statistically significant. In the adjusted models, we excluded all missing data a priori (complete-case analysis) and considered age and sex to be the main study confounders.^{22,24} To test the robustness of our findings regarding the exclusion of missing data, we did a missing indicator analysis (post-hoc), including missing data as a category in the multiple logistic regression models. Also, considering that 18 years is the legal age in Brazil, we did stratified analyses (pre-specified) for individuals aged 10–17 years (hereafter referred to as adolescents) and 18–24 years (hereafter referred to as young adults) to test if factors associated with unfavourable treatment outcomes varied with age. Finally, we did an exploratory descriptive analysis to investigate the extent to which young people with tuberculosis are included in support strategies, including government cash transfers, contact tracing, and treatment supervision. Data management and statistical analysis were done using Stata version 16.0.

Role of the funding source

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

Results

Between Jan 1, 2015, and Dec 31, 2018, 67 360 young people with tuberculosis were notified to SINAN. 41 870 young people were included in the final study population, with 25 490 (38%) of notifications excluded using the study exclusion criteria (figure 1).

The study cohort mostly included young adults aged 18–24 years (n=33 044; 79%), male individuals (n=27 346; 65%), and individuals identifying with Black (n=4895; 13%) or Brown (n=20 307; 52%) skin colour (table 1). Approximately half of the individuals (n=17 383; 53%) had lower educational attainment than their peers. Tobacco use (n=5743; 15%), alcohol misuse (n=3132; 8%), and illicit drug use (n=5976; 15%) were prevalent. 1909 (5%) individuals had a known diagnosis of HIV at the time of diagnosis. Most participants lived in urban settings (n=25 503; 89%), and approximately half were living in the southeast of Brazil (n=21 184; 51%). 2206 (10%) individuals were directly enrolled in government cash transfers. 8273 (16%) individuals were deprived of their liberty (ie, were incarcerated).

Most young people included in this study were diagnosed with pulmonary tuberculosis (n=37 123; 89%). Reporting of diagnostic investigations (smear microscopy and chest radiography) were limited by missing data. However, of those with available data, most had abnormal chest radiography findings (n=26 277; 94%) or positive baseline smear microscopy (n=23 169; 76%). Positive baseline smear microscopy and abnormal chest radiography were predominantly seen in patients with pulmonary tuberculosis (positive smear microscopy: n=23 100, 99%; abnormal chest radiography: n=23 975, 91%).

7024 (17%) of the young people with tuberculosis had unfavourable treatment outcomes (table 1). The univariate analyses showed that the following participant groups had a higher likelihood of unfavourable treatment outcome: young adults (OR 1.74, 95% CI 1.62–1.87), male individuals (1.37, 1.30–1.45), those identifying with Black (1.62, 1.48–1.76) or Brown (1.39, 1.31–1.48) skin colour, those with lower educational attainment than peers (1.83, 1.72–1.95), those reporting tobacco use (2.03, 1.90–2.17), those reporting alcohol misuse (2.38, 2.20–2.59), those reporting illicit drug use (2.88, 2.70–3.06), those with HIV (4.17, 3.79–4.59), those with diabetes (1.52, 1.20–1.93), those living in urban areas (1.57, 1.40–1.77), and those experiencing homelessness (7.81, 6.40–9.53; figure 2). Conversely, some groups were less likely to have an unfavourable treatment outcome in the univariate analyses, namely those identifying as Indigenous (0.76, 0.58–0.99), those receiving government cash transfers (0.78, 0.69–0.89),

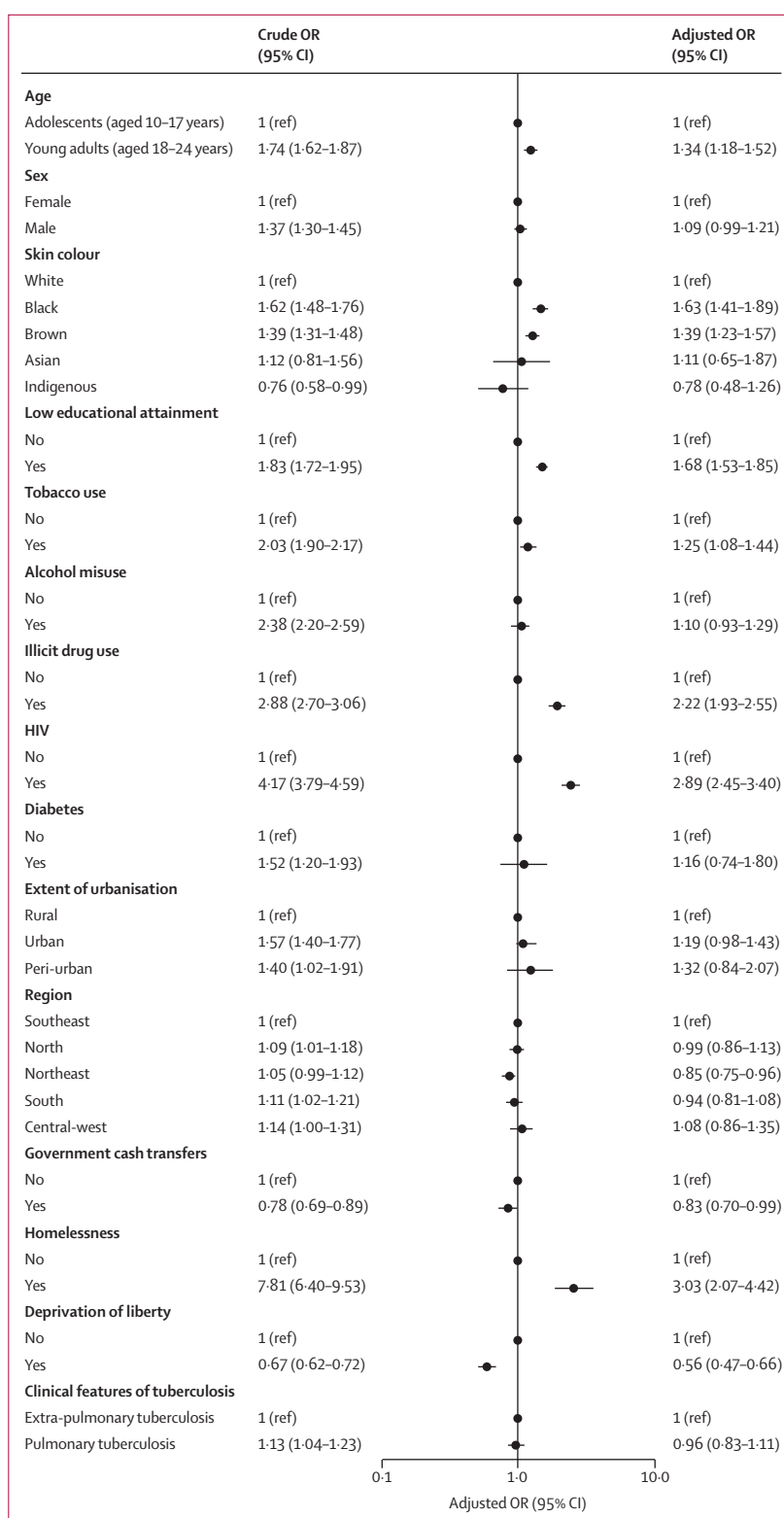


Figure 2: Associations between participant characteristics and unfavourable tuberculosis treatment outcomes

Associations were estimated by a complete case analysis (n=15 050), using univariate and multivariate logistic regression models. OR=odds ratio.

	Adolescents (10–17 years)	Young adults (18–24 years)
Government cash transfers* (n=22 668)		
No	4185 (83%)	16 277 (92%)
Yes	880 (17%)	1326 (8%)
Contact tracing done (n=36 867)		
No	2401 (31%)	8435 (29%)
Yes	5418 (69%)	20 613 (71%)
Treatment supervision provided (n=32 640)		
No	3241 (48%)	12 437 (48%)
Yes	3514 (52%)	13 448 (52%)

Data are n (%). *For the government cash transfer variable, there were similar proportions of missing data for both adolescents (43% [3761/8826] missing data) and young adults (47% [15 441/33 044] missing data).

Table 2: The inclusion of adolescents and young adults with tuberculosis in individual support strategies (excluding missing data)

and those deprived of liberty (0.67, 0.62–0.72). In the adjusted complete case analysis, some groups were more likely to have unfavourable treatment outcomes, namely young adults (adjusted OR 1.34, 1.18–1.52), those identifying with Black (1.63, 1.41–1.89) or Brown (1.39, 1.23–1.57) skin colour, those with lower educational attainment than peers (1.68, 1.53–1.85), those reporting tobacco use (1.25, 1.08–1.44), those reporting illicit drug use (2.22, 1.93–2.55), those with HIV (2.89, 2.45–3.40), and those experiencing homelessness (3.03, 2.07–4.42). Conversely, young people enrolled in government cash transfers (0.83, 0.70–0.99) or those deprived of their liberty (0.56, 0.47–0.66) were less likely to have unfavourable treatment outcome.

When investigating the extent to which young people with tuberculosis were included in individual support strategies (table 2), adolescents were more likely to be included in government cash transfers (n=880; 17%) than young adults (n=1326; 8%). There were similarly low degrees of treatment supervision in adolescents (n=3514; 52%) and young adults (n=13 448; 52%). Approximately a third of adolescents (n=2401; 31%) and young adults (n=8435; 29%) were included in onward contact tracing efforts.

In stratified analyses (table 3, table 4), the magnitude of association for those identifying with Black (adjusted OR 2.20, 95% CI 1.50–3.22) or Brown (1.61, 1.17–2.23) skin colour, low educational attainment (2.18, 1.71–2.78), illicit drug use (3.32, 2.06–5.35), and HIV (4.63, 2.81–7.63) was greater for adolescents than young adults. Government cash transfers were only significantly associated with a smaller likelihood of unfavourable treatment outcome for adolescents (0.66, 0.46–0.93). However, male sex (1.12, 1.00–1.25), tobacco use (1.26, 1.08–1.46), and homelessness (3.32, 2.22–4.96) were only significantly associated with unfavourable treatment outcome for young adults. Deprivation of liberty was only protective for young adults (0.55, 0.47–0.65).

Discussion

To the best of our knowledge, this study is the first national evaluation of young people with tuberculosis in Brazil. Our study population predominantly included male individuals, young adults, individuals identifying with Black or Brown skin colour, and individuals living in urban areas. Almost a fifth of young people with tuberculosis were deprived of their liberty and approximately half had lower educational attainment.

Young adults (aged 18–24 years), those identifying with Black or Brown skin colour, those with lower educational attainment, those reporting tobacco use, those reporting illicit drug use, those with HIV positivity, and those experiencing homelessness had an increased likelihood of unfavourable tuberculosis treatment outcome. Young people in receipt of government cash transfers or deprived of their liberty had a decreased likelihood of having unfavourable tuberculosis treatment outcomes. However, there was some discrepancy in the social and health factors associated with unfavourable treatment outcome for adolescents and young adults. Despite the social and health vulnerabilities of young people with newly diagnosed tuberculosis in Brazil, approximately half (52%) of the young people were provided with treatment supervision and a minority (10%) received government cash transfers.

An estimated 17% (7024 of 41870) of young people with tuberculosis in this cohort had an unfavourable tuberculosis treatment outcome, which falls behind the WHO End TB Strategy targets.¹⁵ However, the rate of unfavourable treatment outcome in young people observed in this study is still lower than the rate observed in individuals notified with tuberculosis over the past decade in Brazil (202 713 [21%] of 970 774 individuals between 2010 and 2020).¹⁶ Other studies have found that the proportion of tuberculosis-related deaths continually increases from childhood (<10 years) to older adulthood (≥50 years), with a substantially higher rate of atypical features of tuberculosis, more adverse drug reactions, and higher tuberculosis-related mortality for older adults (≥65 years) than their younger counterparts (<65 years), which might in part explain our findings.^{25,26} It is also possible that the underdiagnosis or under-reporting of disseminated tuberculosis could explain the lower mortality rate observed in young people, as seen in another study in the Philippines.²⁷ Finally, there might be discrepancies in the definition of unfavourable tuberculosis treatment outcome contributing to the variation seen across studies.

Consistent with other studies, we found that new cases of tuberculosis and likelihood of unfavourable outcome were highest in young adults.¹³ The overarching majority of new cases occurred in male individuals. However, being male was only significantly associated with an increased likelihood of unfavourable treatment outcome for young adults. In the adult population, men are at a substantially higher risk of contracting and dying from

	Adolescents aged 10–17 years (n=3862)	Young adults aged 18–24 years (n=12 966)
Sex		
Female	1 (ref)	1 (ref)
Male	0.94 (0.76–1.16)	1.13 (1.02–1.26)
Skin colour		
White	1 (ref)	1 (ref)
Black	2.07 (1.44–2.98)	1.44 (1.24–1.68)
Brown	1.73 (1.28–2.34)	1.32 (1.17–1.50)
Asian	2.54 (0.92–7.03)	0.88 (0.49–1.56)
Indigenous	0.77 (0.33–1.79)	0.79 (0.46–1.36)
Low educational attainment		
No	1 (ref)	1 (ref)
Yes	2.06 (1.64–2.59)	1.62 (1.47–1.79)
Tobacco use		
No	1 (ref)	1 (ref)
Yes	1.19 (0.73–1.93)	1.27 (1.10–1.46)
Alcohol misuse		
No	1 (ref)	1 (ref)
Yes	0.94 (0.53–1.68)	1.12 (0.95–1.31)
Illicit drug use		
No	1 (ref)	1 (ref)
Yes	3.66 (2.36–5.70)	2.11 (1.84–2.42)
HIV		
No	1 (ref)	1 (ref)
Yes	4.52 (2.85–7.17)	2.80 (2.39–3.29)
Diabetes		
No	1 (ref)	1 (ref)
Yes	1.19 (0.44–3.22)	1.40 (0.91–2.14)
Extent of urbanisation		
Rural	1 (ref)	1 (ref)
Urban	1.13 (0.75–1.70)	1.29 (1.06–1.57)

(Table 3 continues in next column)

	Adolescents aged 10–17 years (n=3862)	Young adults aged 18–24 years (n=12 966)
(Continued from previous column)		
Peri-urban	0.79 (0.16–3.93)	1.27 (0.81–2.01)
Region		
Southeast	1 (ref)	1 (ref)
North	0.83 (0.62–1.13)	0.96 (0.83–1.11)
Northeast	0.84 (0.63–1.11)	0.83 (0.73–0.94)
South	0.92 (0.65–1.31)	0.94 (0.81–1.09)
Central-west	1.62 (0.97–2.73)	1.02 (0.81–1.29)
Homelessness		
No	1 (ref)	1 (ref)
Yes	1.13 (0.33–3.86)	3.52 (2.38–5.21)
Deprivation of liberty		
No	1 (ref)	1 (ref)
Yes	1.15 (0.53–2.52)	0.56 (0.48–0.66)
Clinical features of tuberculosis		
Extra-pulmonary tuberculosis	1 (ref)	1 (ref)
Pulmonary tuberculosis	0.71 (0.54–0.94)	0.97 (0.83–1.13)

Data are adjusted odds ratio (95% CI). Associations were estimated by complete case analyses of adolescents and young adults (excluding the government cash transfers variable), using multivariate logistic regression models.^ç

Table 3: Associations between participant characteristics and unfavourable tuberculosis treatment outcomes—excluding the government cash transfers variable

tuberculosis than women, whereas women face distinct challenges to access tuberculosis services and care, including stigma.^{28,29}

Our study findings with respect to skin colour and race were similar to other studies that showed that those identifying with Black or Brown skin colour had higher odds of loss to follow-up and death from tuberculosis in Brazil than those with White skin colour.²² These findings probably relate to structural racism that persists for people identifying with Black or Brown skin colour, with respect to education, employment, occupation, and income level, which are distal determinants of tuberculosis.³⁰ Concerningly, the association between race and unfavourable treatment outcome persisted for both adolescents and young adults in stratified analyses, emphasising the need for an intersectional approach from policy makers and clinicians.

Low educational attainment was associated with unfavourable treatment outcome in this study, and the direction and magnitude of this association persisted for both adolescents and young adults in stratified analyses.

Similarly, among adults with tuberculosis, participation or completion of higher education was associated with lower likelihood of loss to follow-up compared to those who had not completed higher education.²² Indeed, secure employment, higher income level, and higher socioeconomic status are largely determined by education level. Other studies have also emphasised the importance of health literacy in the context of tuberculosis infection, especially in high-burden settings reliant on passive case finding. One study in Lima, Peru, found that key determinants of tuberculosis-related health literacy were occupation and socioeconomic status, with patients living in poverty being four times more likely to have low health literacy than those not living in poverty.³¹ The effect of tuberculosis infection, time spent at appointments, and tuberculosis treatment on a young person's educational attainment, onward employment, and income level are also highly relevant, but beyond the remit of this study.

The prevalence of illicit drug use was relatively high in our cohort and appeared to be more common than alcohol misuse. These findings are substantiated by downward trends in alcohol consumption for adolescents attending public schools in Brazil between 1989 and 2010.³² Accordingly, drug use is probably increasingly relevant for young people with tuberculosis. Deiss and colleagues³³ also described the increasing burden of tuberculosis for urban subpopulations, in particular people who use drugs, and found that those using illicit

	Adolescents aged 10–17 years (n=3431)	Young adults aged 18–24 years (n=11 619)
Sex		
Female	1 (ref)	1 (ref)
Male	1.04 (0.82–1.30)	1.12 (1.00–1.25)
Skin colour		
White	1 (ref)	1 (ref)
Black	2.20 (1.50–3.22)	1.54 (1.31–1.82)
Brown	1.61 (1.17–2.23)	1.36 (1.19–1.55)
Asian	2.59 (0.86–7.83)	0.94 (0.52–1.70)
Indigenous	0.81 (0.33–1.99)	0.74 (0.41–1.33)
Low educational attainment		
No	1 (ref)	1 (ref)
Yes	2.18 (1.71–2.78)	1.60 (1.44–1.78)
Tobacco use		
No	1 (ref)	1 (ref)
Yes	1.15 (0.68–1.92)	1.26 (1.08–1.46)
Alcohol misuse		
No	1 (ref)	1 (ref)
Yes	0.99 (0.55–1.81)	1.11 (0.93–1.31)
Illicit drug use		
No	1 (ref)	1 (ref)
Yes	3.32 (2.06–5.35)	2.13 (1.84–2.46)
HIV		
No	1 (ref)	1 (ref)
Yes	4.63 (2.81–7.63)	2.74 (2.30–3.25)
Diabetes		
No	1 (ref)	1 (ref)
Yes	0.78 (0.22–2.75)	1.23 (0.76–1.97)
Extent of urbanisation		
Rural	1 (ref)	1 (ref)
Urban	1.03 (0.67–1.60)	1.21 (0.99–1.49)
Peri-urban	0.78 (0.15–4.12)	1.37 (0.86–2.21)
Region		
Southeast	1 (ref)	1 (ref)
North	0.81 (0.58–1.13)	1.04 (0.89–1.20)
Northeast	0.86 (0.64–1.17)	0.85 (0.75–0.98)
South	0.82 (0.57–1.19)	0.96 (0.82–1.12)
Central-west	1.60 (0.90–2.83)	1.02 (0.80–1.31)
Homelessness		
No	1 (ref)	1 (ref)
Yes	1.26 (0.35–4.46)	3.32 (2.22–4.96)

(Table 4 continues in next column)

drugs have physiological, environmental, and social risk factors that increase their likelihood of onward tuberculosis transmission, loss to follow-up, and death during treatment. There is evidently a diversity of illicit drug use in terms of type of drug taken, quantity used, and regularity of use. These different drug use practices might be associated with a range of risk factors and consequences, and hence require various different potential mitigation strategies. Therefore, it would be useful to better understand the specific drug use

	Adolescents aged 10–17 years (n=3431)	Young adults aged 18–24 years (n=11 619)
(Continued from previous column)		
Deprivation of liberty		
No	1 (ref)	1 (ref)
Yes	1.28 (0.58–2.85)	0.55 (0.47–0.65)
Government cash transfers		
No	1 (ref)	1 (ref)
Yes	0.66 (0.46–0.93)	0.91 (0.75–1.11)
Clinical features of tuberculosis		
Extra-pulmonary tuberculosis	1 (ref)	1 (ref)
Pulmonary tuberculosis	0.73 (0.54–0.98)	1.03 (0.87–1.22)

Data are adjusted odds ratio (95% CI). Associations were estimated by complete case analyses of adolescents and young adults (including the government cash transfers variable), using multivariate logistic regression models.

Table 4: Association between participant characteristics and unfavourable tuberculosis treatment outcomes—including government cash transfers variable

practices and their distinct associations with unfavourable treatment outcome for young people.

5.05% of our study population was HIV positive, as compared with a prevalence of 0.04% in Brazil. There is little evidence showing the prevalence of tuberculosis–HIV co-infection among young people worldwide, with HIV-positive estimates varying between 10% and 60% for younger children with tuberculosis.³⁴ In this study, young people with HIV had approximately three times higher odds of unfavourable tuberculosis treatment outcome. Our finding that HIV-co-infection was associated with an increased likelihood of unfavourable tuberculosis treatment outcome is similar to that of other studies.³⁵ A systematic review of prediction models for pulmonary tuberculosis outcomes in adults also found that HIV was a common predictor of unfavourable treatment outcome.³⁶ Tuberculosis accounts for a quarter of HIV-related deaths globally, and management and care of young people with tuberculosis–HIV co-infection is often challenging, especially among those with advanced HIV.^{37,38} Improved access to well integrated tuberculosis and HIV services is crucial to improve outcomes for people living with HIV and diagnosed with tuberculosis, especially for affected adolescents and young adults.

Experiencing homelessness was strongly associated with unfavourable treatment outcome in this study, although the effect size persisted only for young adults in the stratified analyses. It is possible that there are hidden confounding variables influencing the association between homelessness and treatment outcome; homelessness might be considered an extreme life condition for young adults, and might relate to lack of shelter, malnutrition, overcrowding, and extreme poverty.³⁹ Similar findings have previously been reported for adults with tuberculosis who are experiencing homelessness: in

São Paulo, Brazil, homeless adults with tuberculosis were more likely to experience loss to follow-up and death than the general population with tuberculosis.³⁹

Conversely, deprivation of liberty was associated with a lower likelihood of unfavourable treatment outcome in our study—although this association only persisted for young adults. These findings align with those from Maciel and Reis-Santos,²² who suggested that adults with tuberculosis in Brazilian prisons were less likely to be lost to follow-up or die, probably because of closer institutionalised treatment supervision, focused tuberculosis screening, and contact tracing. It remains concerning that deprivation of liberty was prevalent among our study cohort. In 2014, it was estimated that juvenile detention centres in Brazil exceeded their maximum capacity by over 20%, which likely contributes to the risk of tuberculosis infection for young people.⁴⁰

Young people who received governmental cash transfers had a decreased likelihood of unfavourable treatment outcome in our study, although this association was only detected for adolescents in the stratified analyses. The relevance of the stratified analysis is unclear given the extent of missing data for the government cash transfer variable in young adults. Adolescents are more likely to still reside at home and it is possible that other family members might be in receipt of additional government social protection schemes; therefore enhancing the observed effect of cash transfers. In this study, cash transfers were not specific to tuberculosis treatment programmes, and relate to separate inclusion criteria regarding household income and social deprivation. Young people were not adequately included in government cash transfers in this cohort, and this might reflect subtle disparities in accessibility and perceived eligibility or deservedness of young people to this form of social protection.

The scope of social protection, and specifically government cash transfers, is relevant to tuberculosis elimination efforts among young people. People with tuberculosis are susceptible to economic shocks and might be threatened by catastrophic costs during tuberculosis treatment.⁴¹ Our findings reinforce that targeting cash transfers to people with tuberculosis and their households can increase household income, reduce food insecurity, and improve tuberculosis treatment success rates.^{22,24,41–43} A systematic literature review and meta-analysis on the effects of social protection on tuberculosis treatment outcomes in low-income and middle-income settings, and in countries with high tuberculosis burden, found that social protection programmes were associated with tuberculosis treatment success (risk ratio [RR] 1.09, 95% CI 1.03–1.14) and cure (RR 1.11, 1.01–1.22) as well as with reduced risk of loss to follow-up (RR 0.63, 0.45–0.89); yet these programmes were not significantly associated with treatment failure or mortality.⁴⁴

Young people in more vulnerable groups are often underserved; and, as this study suggests, young people

with tuberculosis—in particular those experiencing homelessness, living with HIV, using illicit drugs, or having lower educational attainment—were most likely to have an unfavourable treatment outcome. de Oliveira and colleagues⁴⁵ sought to aggregate some of these characteristics as markers of extreme vulnerability, and found that adolescents presenting with either homelessness, incarceration, tobacco use, illicit drug use, or alcohol misuse were three times more likely to have an unfavourable outcome. However, further work is needed to better understand how to target young people with differing characteristics of extreme vulnerability through an intersectional approach in national tuberculosis policy, especially in the context of the ongoing COVID-19 pandemic and its effects on health and social systems.

Our study is also subject to limitations. This study used secondary clinical registry data that contained a considerable proportion of missing data (up to 43% in the government cash transfer variable). Young people with tuberculosis who had missing values attributed to their skin colour, education level, HIV status, or homelessness were significantly more likely to have an unfavourable tuberculosis treatment outcome in the sensitivity analysis. Therefore, the exclusion of missing values might have resulted in the underestimation of the association found for these variables of interest. Additionally, São Paulo state did not report data relating to all new variables introduced in 2015, including the government cash transfer variable. There is, therefore, a risk of bias and underestimation of the association found between the government cash transfer variable and unfavourable treatment outcome, particularly for young adults, in the stratified analyses. Although the extent and nature of missing data might limit the generalisability of our findings, the similar point estimates for adjusted odds ratios in the complete-case and missing indicator analyses suggest that there is little possibility of the missing data having interfered in our results (appendix pp 2–3).

We did not have information on important confounders, such as household income, in addition to information relating to HIV diagnosis (including viral load, CD4 count, and time of initiation and co-administration of antiretroviral therapy). Additionally, it is unclear if loss of information about individuals who were transferred to other health-care centres was due to clinical need or change of home address due to unforeseen circumstances, and might have resulted in the inclusion of healthier or less vulnerable study participants in this study. Although we included change in treatment regimen ($n=125$) as an unfavourable treatment outcome, others might argue that changes in treatment regimen are common in usual tuberculosis management and care. However, this inclusion is unlikely to have resulted in the overestimation of the prevalence of unfavourable treatment outcomes in our study population.

See Online for appendix

Amid upward trends in tuberculosis incidence for young adults, this study found that almost a fifth of young people with tuberculosis in Brazil had an unfavourable treatment outcome between 2015 and 2018. Race, poverty, and comorbidities were associated with a higher likelihood of unfavourable outcome, whereas being in receipt of government cash transfers was found to be protective. Our findings emphasise the need for individualised, patient-centred, and equitable tuberculosis care for young people.

Contributors

LC, KSA, JMP, and TW conceptualised the Article. LC, JMP, and TW were responsible for the study design. LC and JMP did the data collection. KSA, JMP, and TW contributed materials and analysis tools. LC, KSA, JMP, and TW analysed the data. LC and JMP created the figures. LC drafted the first version of the Article. LC, KSA, JMP, and TW reviewed and edited the manuscript. KSA, JMP, and TW supervised the study process. TW acquired funding. All authors read and met the ICMJE criteria for authorship and agree with the results and conclusions. LC and JMP accessed and verified the study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The secondary level de-identified clinical registry data used in this study, and a relevant data dictionary defining each field in the set, will be made available to others and can also be retrieved or downloaded directly using the references provided in the study methodology. The data will be made available with publication, and is already openly accessible and available through SINAN DATASUS, or might alternatively be obtained through contact with the corresponding author.

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