Background: Pregnancy increases the risk of tuberculosis (TB), however, data on TB epidemiology in pregnant women are limited. Aim: To guide possible interventions, we analysed risk factors for TB in pregnant and post-partum women.

Methods: We conducted a nationwide retrospective register-based case–control study from January 1990 to December 2018 in Denmark. Cases were women diagnosed with TB during their pregnancy or in the post-partum period. We selected two control groups: pregnant or post-partum women without TB, and non-pregnant women with TB. Differences were assessed by chi-squared or Fisher’s exact test. Risk factors for TB were identified through logistic regression and estimated by odds ratio (OR).

Results: We identified 392 cases, including 286 pregnant and 106 post-partum women. Most were migrants (n = 366; 93%) with a shorter median time spent in Denmark (2.74 years; interquartile range (IQR): 1.52–4.64) than non-pregnant TB controls (3.98 years; IQR: 1.43–8.51). Cases less likely had a Charlson comorbidity index ≥ 2 compared with non-pregnant TB controls (p < 0.0001), and had no increased risk of severe disease (p = 0.847). Migrants from other World Health Organization regions than Europe, especially Africa (OR: 1.87; 95%CI: 1.25–2.81) had persistently higher odds of TB. Conclusions: In Denmark, the risk of TB in pregnant and post-partum women is increased in migrant women who have stayed in the country a median time of approximately 3 years. We recommend increased focus on TB risk during pregnancy and suggest evaluating targeted TB screening of selected at-risk pregnant women to promote early case finding and prevent TB among mothers and their newborn children.

Introduction

The true global burden of tuberculosis (TB) during pregnancy is not known, but it is estimated that there are more than 200,000 cases per year [1]. Early diagnosis of TB among pregnant women is essential because TB poses a risk of serious illness not only for the pregnant woman but also in particular for the newborn child [2-5]. Pregnancy increases the risk of progressing from TB infection (TBI) to active TB [6] by different hormonal and immunological changes [7-9]. This shift leads to impaired cellular immunity and thus increased susceptibility to certain infections such as TB [7,10]. A recent study from Sweden found an increased risk of TB during pregnancy and the post-partum period among migrants from TB high-incidence countries [11], in line with findings from the United Kingdom (UK) [12]. Interestingly, screening of eligible pregnant migrants from countries with high TB incidence has been implemented in the Swedish antenatal care programme with a high yield of both TBI and TB case detection [13].

TB among pregnant and post-partum women has not been highly prioritised in TB research and TB control programmes [5,14]. Across Europe, there are very variable policies for screening migrants and other TB risk groups, and only few countries have specific guidelines addressing pregnancy and TB risk [15,16]. In Denmark, there are limited data on pregnancy and TB, and there are no guidelines on the control and management of TB in pregnant migrants from high-incidence countries. In this nationwide study, we describe women who are diagnosed with TB during pregnancy and the post-partum period in Denmark and analyse risk factors, in order to guide future public health policies.
**Methods**

**Setting**

In Denmark, healthcare is free for all residents, including antenatal care, TB diagnostics and treatment. It is mandatory to notify TB to the health authorities and data are systematically registered in the national TB Surveillance Register (TBSR), centrally hosted at the Department of Infectious Diseases Epidemiology and Prevention, Statens Serum Institut (SSI). All TB diagnostics are centralised at the International Reference Laboratory of Mycobacteriology (IRLM), SSI. Residents in Denmark are assigned a unique central personal identification (CPR) number in the Civil Registration System (CRS). This CPR number can be used to individually track and link information in national registries and databases.

**Design and study population**

This was a nationwide retrospective register-based case–control study conducted in Denmark from January 1990 through December 2018. Cases were women diagnosed with TB during pregnancy or during the post-partum period, who were compared with two control groups; pregnant or post-partum women from the general population without TB, and non-pregnant/non-post-partum women with TB.

**Data generation**

TB cases were identified in the TBSR, from which information on ethnicity, country of origin, country of infection, and sources of infection was extracted. To avoid duplicate TB cases, a case could only count once during a 12-month period in accordance with World Health Organization (WHO)/European Centre for Disease Prevention and Control (ECDC) guidelines [17]. The pregnant TB cases were defined as women who had been diagnosed with TB up to 9 months before giving birth. Post-partum TB cases were defined as women who were diagnosed with TB up to 12 months following delivery. The National Patient Register (NPR) was used to identify pregnant and post-partum cases as this registry contains diagnoses codes and time of diagnoses according to the International Classification of Diseases (ICD) 8 (1989–1993) and ICD 10 (after 1993). From the NPR, we extracted information on hospitalisations/outpatient hospital visits and length of admission in days. In addition, diagnoses codes were used to calculate the Charlson comorbidity index (CCI) [18]. We obtained information on culture-verified TB cases from the IRLM, SSI. From the CRS, we obtained information on date of birth and death, sex, place of residency, and date of immigration into Denmark for migrants. From the National Registry of Causes of Deaths, we extracted information on death causes.
| Characteristic                                      | Cases  | Pregnant/post-partum controls | TB controls | p*  |
|---------------------------------------------------|--------|------------------------------|-------------|-----|
|                                                   | n = 392 | n = 6,514                    | n = 2,316   |     |
| Age group (years)                                 |        |                              |             |     |
| 15–24                                            | 107    | 27                           | 2,187       | 20  |
|                                                  | 25–34  | 230                          | 2,697       | 41  |
|                                                  | 35–50  | 55                           | 2,630       | 39  |
| Total^b                                          | 392    | NA^c                          | 6,514       | NA^c|
| Category^d                                       |        |                              |             |     |
| Danes^d                                          | 26     | 7                            | 5,799       | 89  |
|                                                  | 366    | 93                           | 715         | 11  |
| Total^b                                          | 392    | NA^c                          | 6,514       | NA^c|
| Country or WHO region of origin                   |        |                              |             |     |
| Denmark                                          | 26     | 7                            | 5,799       | 89  |
|                                                  | 34     | 9                            | 357         | 5   |
| Region of the Americas                            | 1      | 0                            | 13          | 0   |
| African Region                                    | 228    | 58                           | 59          | 1   |
| Eastern Mediterranean Region                      | 49     | 13                           | 190         | 3   |
| South-east Asian Region                           | 26     | 7                            | 37          | 1   |
| Western Pacific Region                            | 28     | 7                            | 58          | 1   |
| Total^b                                          | 392    | NA^c                          | 6,514       | NA^c|
| Time from immigration to Denmark until TB diagnosis (years)^e |       |                              |             |     |
| 0–2                                              | 200    | 55                           | 0           | 0   |
|                                                  | 166    | 29                           | 0           | 0   |
| 6–10                                             | 39     | 11                           | 0           | 0   |
| ≥ 11                                             | 21     | 6                            | 0           | 0   |
| Total^b                                          | 366    | NA^c                          | 0           | NA^c|
| Number of persons in household                    |        |                              |             |     |
| 1                                                | 4      | 1                            | 534         | 8   |
| 2–3                                              | 111    | 28                           | 3,158       | 48  |
| 4–5                                              | 153    | 39                           | 2,484       | 38  |
| 15                                               | 122    | 31                           | 338         | 5   |
| Total^b                                          | 390    | NA^c                          | 6,514       | NA^c|
| Educational level                                 |        |                              |             |     |
| Elementary school                                 | 180    | 53                           | 2,477       | 39  |
| High school                                       | 65     | 19                           | 1,283       | 20  |
| Short higher                                      | 68     | 20                           | 1,623       | 25  |
| University degree                                 | 27     | 8                            | 997         | 16  |
| Total^b                                          | 340    | NA^c                          | 6,380       | NA^c|

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NA: not applicable; TB: tuberculosis; WHO: World Health Organization.

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a Differences between cases and controls were estimated by Chi-squared test or Fischer’s exact test for categorical variables.

b Except for the subsection entitled ‘Comorbidities’, the total of a column in each horizontal subsection represents the sum of the numbers in that column. This sum is used as the denominator for the percentages presented in the next column. Because totals are based only on the numbers of persons with available data, they may differ from the totals provided in the Table header, for the overall columns. For the subsection entitled ‘Comorbidities’ the total of a given column does not represent the sum of numbers in that column, but only indicates the total used for the percentages in the next column.

c The totals of percentages, which are not presented, can be different from 100, because of rounding issues.

d The category is based on the geographical area of origin. Because Greenland has a different TB epidemiology than Denmark, Greenlanders (comprising people born in Greenland or with at least one parent born in Greenland) are classified as migrants in the study. Among cases, seven women were Greenlanders. There were no Greenlanders among pregnant/post-partum controls, whereas there were 210 Greenlanders among the TB controls.

e Only calculated for immigrants having a migration date in the Civil Registration System.
The generation of the two control groups is illustrated in Figure 1. The first control group ‘pregnant/post-partum controls’ was generated from a preselected control group containing controls without TB from the general population, matched on sex and age to all TB cases. From this preselected control group, we included all women who had a diagnosis code pertaining to labour (ICD8: 650–662, ICD10: DO80–DO84) and who were in the same age range as cases (16–49 years).

The second control group ‘TB controls’ was generated from the TB population and defined as women aged 16–49 years who had not given birth up to 9 months after the date of a TB diagnosis and who had not been diagnosed with TB up to 12 months after delivery.

From the Statistics Denmark Database, containing most nationwide registries, we extracted information of family structure, highest educational attainment, employment status and income for cases and controls. Data from registers and databases were linked by the CPR number and subsequently anonymised. Data were handled by secured individual access to Statistics Denmark.

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**Table 1b**

Characteristics of women diagnosed with tuberculosis while pregnant or in the post-partum period (cases) compared with pregnant/post-partum controls and tuberculosis controls, Denmark, 1990–2018 (n = 9,222)

| Characteristic                  | Cases        | Pregnant/post-partum controls | TB controls | p*  |
|--------------------------------|--------------|-------------------------------|-------------|-----|
|                                | n = 392 %    | n = 6,514 %                  | n = 2,316 % |     |
| **Employment**                 |              |                               |             |     |
| Employed                       | 44 11        | 4,370 67                     | 576 25      |     |
| Unemployed                     | 9 2          | 329 5                       | 108 5       | <0.0001 |
| On leave                       | 11 3         | 228 4                       | 74 3        |     |
| Education                      | 5 1          | 841 13                      | 217 9       |     |
| Disability pension             | 3 1          | 135 2                       | 202 9       |     |
| Cash benefit recipient         | 230 59       | 402 6                       | 693 30      |     |
| Unknown/other                  | 90 23        | 209 3                       | 446 19      |     |
| Totala                         | 392 NA        | 6,514 NA                     | 2,316 NA    | NA  |
| **Yearly income (EUR)**        |              |                               |             |     |
| <15,000                        | 364 93       | 2,657 41                    | 1,876 81    | <0.0001 |
| 15,000–29,000                  | 15 4         | 1,745 27                    | 237 10      |     |
| 30,000–34,000                  | 10 3         | 1,443 22                    | 141 6       |     |
| ≥45,000                        | 3 1          | 669 10                      | 62 3        |     |
| Totala                         | 392 NA        | 6,514 NA                     | 2,316 NA    | NA  |
| **Charlson comorbidity index** |              |                               |             |     |
| 0                              | 292 75       | 5,006 77                    | 1,363 59    | <0.0001 |
| 1                              | 57 15        | 828 13                      | 395 17      |     |
| ≥2                             | 43 10        | 680 10                      | 558 24      |     |
| Totala                         | 392 NA        | 6,514 NA                     | 2,316 NA    | NA  |
| **Comorbidities**              |              |                               |             |     |
| Diabetes                       | 18 5         | 183 3                       | 144 6       | <0.0001 |
| HIV                            | 8 2          | 4 0                         | 94 4        |     |
| HBV                            | 10 3         | 16 0                        | 64 3        |     |
| HCV                            | 1 0          | 21 0                        | 63 3        |     |
| Totala                         | 392 NA        | 6,514 NA                     | 2,316 NA    | NA  |

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NA: not applicable; TB: tuberculosis; WHO: World Health Organization.

a Differences between cases and controls were estimated by Chi-squared test or Fisher’s exact test for categorical variables.

b Except for the subsection entitled ‘Comorbidities’, the total of a column in each horizontal subsection represents the sum of the numbers in that column. This sum is used as the denominator for the percentages presented in the next column. Because totals are based only on the numbers of persons with available data, they may differ from the totals provided in the Table header, for the overall columns. For the subsection entitled ‘Comorbidities’ the total of a given column does not represent the sum of numbers in that column, but only indicates the total used for the percentages in the next column.

c The totals of percentages, which are not presented, can be different from 100, because of rounding issues.

d The category is based on the geographical area of origin. Because Greenland has a different TB epidemiology than Denmark, Greenlanders (comprising people born in Greenland or with at least one parent born in Greenland) are classified as migrants in the study. Among cases, seven women were Greenlanders. There were no Greenlanders among pregnant/post-partum controls, whereas there were 210 Greenlanders among the TB controls.

e Only calculated for immigrants having a migration date in the Civil Registration System.
In this study, cases and controls were categorised as either migrants or Danes, according to their geographical area of origin. Danes were defined as being born in Denmark with both parents also born in Denmark. Migrants were defined as persons born outside of Denmark or persons with one or both parents born outside of Denmark. Denmark and Greenland are constituents of the Kingdom of Denmark, however the incidence of TB differs in these two parts, as the incidence is much higher in Greenland (88 per 100,000 population per year) [19], than in Denmark (5 per 100,000 population per year) [20]. As such, persons born in Greenland, or with one or both parents born in Greenland were classified as migrants for the purpose of the study.

Countries of origin were stratified into the six WHO regions: European Region, Region of the Americas, African Region, Eastern Mediterranean Region, South-East Asian Region and Western Pacific Region. Generally, and in accordance with WHO guidelines [21], pulmonary TB (PTB) was defined as TB involving the lung parenchyma and/or tracheobronchial tree including miliary TB and mixed PTB/extrapulmonary TB (EPTB). EPTB was defined as TB involving organs other than the lungs. Severe TB was defined as having at least two of the following conditions: multiple-organ disease, culture-positive disease, or a long hospital admission of >10 days. To serve as proxies for socioeconomic status (SES) we used highest attained education, employment status and yearly income.

Categorical data were described by numbers and percentages. For data comparisons, differences were assessed by chi-squared test or Fisher’s exact test where appropriate. Continuous variables were presented as medians and 25–75% interquartile range (IQR) and compared by the non-parametric Wilcoxon rank sum test.

Risk factors for TB were assessed among cases and pregnant/post-partum controls. We estimated the risk of TB by logistic regression analyses calculating odds ratio (OR) with 95% confidence interval (CI) using Wald test. Initially we included the following variables: outcome was TB, and exposures were categories according to origin (Danes/migrants; WHO region of origin), years since immigration, CCI, number of persons in household, education, employment and income. However, due to a high number of cases from Africa with missing data for education, the final model was fitted to only include WHO region of origin, CCI, number of persons in household, employment status (employed/unemployed), and income level (low (≤EUR 15,000 per year)/ high (≥EUR 15,000 per year)). We tested for interactions and collinearity, which did not affect the estimates.

Risk factors for severe TB were estimated by comparing cases with TB controls; the outcome was severe TB, exposure variables were category (Danes/migrants), CCI, employment status and income level. Data management and statistical analyses were carried out in SAS version 9.4.
Ethical statement
The study was approved by the Danish Data Protection Agency (J.no 19/04240). No further ethical approval is required in Denmark for registry-based research studies. Data were analysed anonymously and assessed online in the Statistics Denmark’s research database.

Results
Basic demography, socioeconomic status and comorbidities
We identified 392 women who were pregnant (n = 286) or in the post-partum period (n = 106) when diagnosed with TB in Denmark from 1990 to 2018. The majority were migrants (n = 366; 93%), predominantly from Africa (n = 228; 58%) (Table 1). Among migrants, women from Somalia accounted for 54% (n = 199), followed by Pakistan (n = 34; 9%), the Philippines (n = 13; 4%), Vietnam (n = 10; 3%), and Thailand (n = 9; 2%). During the study period, the distribution of the women’s countries of origin varied (Figure 2). From 1993 to 2006, the largest proportion of migrant cases was constituted by African women (n = 202), especially from Somalia (686/202; 92%). The distribution according to geographical area of origin was similar among TB controls, but different from the pregnant/post-partum-controls, of whom 89% were Danes and of whom the majority of migrants was from other European countries (Table 1). Among migrants, the median time in Denmark since immigration was substantially shorter among TB cases (2.74 years; IQR: 1.52–4.64) compared with TB controls (3.98 years; IQR: 1.43–8.51). Generally, cases and TB controls were of significantly lower education, were less employed and had a lower yearly income than pregnant/post-partum controls (Table 1). In contrast to the cases and pregnant/post-partum controls, TB controls more frequently lived in crowded conditions (<5 persons in the household). The majority of cases had no noteworthy comorbidities comparable to pregnant/post-partum controls but were considerably different from the TB controls who had higher CCI (Table 1). Diabetes, HIV and hepatitis were more common among cases and TB controls than among pregnant/post-partum controls (Table 1).

Disease site and severity
More TB controls had PTB and were smear positive compared with cases, however there were no differences in the proportion of severe TB cases in the two groups (Table 2). There were no significant differences in the proportion of cases and controls being hospitalised (50% vs 52% respectively; p = 0.097) or the median lengths of admission (13 days (IQR: 7–20) vs 12 days (IQR: 7–19) respectively; p = 0.88). Mortality was highest among TB controls, though few died from TB (Table 2).

Risk factors
Univariable logistic regression showed high odds of TB among migrants from outside the European Region, living in crowded environments (>5 per household), with low education, who were unemployed or who had low income (Table 3). Due to a high number of missing data for the variable education (n = 186), especially among cases from Africa, this variable was removed when fitting the final model. In the fitted multivariable logistic regression model, we adjusted for persons in household, CCI, employment and income, and found extremely high odds for TB among migrants from Africa (OR: 187) compared with European origin (including Danes and Greenlanders) (Table 3). Being unemployed and having a low yearly income were significantly associated with TB. The multivariable regression model assessing risk of severe TB showed no significant associations for category (Danes/migrants), CCI, employment status or income (Table 4).

Discussion
In this nationwide retrospective case-control study of women diagnosed with TB during pregnancy or in the post-partum period, the vast majority of such women were migrants recently arriving from TB high-burden countries without significant comorbidities and a TB disease severity similar to non-pregnant women with TB. The fact that cases had shorter median time in Denmark since immigration until TB diagnosis compared with TB controls (2.74 vs 3.98 years), may reflect how pregnancy accelerates progression from TBI to active TB.

Table 2
Tuberculosis characteristics in women diagnosed while pregnant or in the post-partum period (cases) compared with tuberculosis controls, Denmark, 1990–2018 (n = 2,708)

| TB characteristic | Cases n = 392 | TB controls n = 2,316 | p* |
|-------------------|--------------|----------------------|----|
| Pulmonary TB      | 205 (52)     | 1,555 (67)           | <0.0001 |
| Smear-positive pulmonary TB | 69 (34) | 706 (45) | 0.0015 |
| Culture positive | 313 (80)     | 1,769 (76)           | 0.1323 |
| INH mono resistance | 21 (5) | 100 (4) | 0.3570 |
| MDR               | 2 (0)        | 10 (0)               | 0.8288 |
| Infected abroad   | 316 (81)     | 1,445 (62)           | <0.0001 |
| Severe TB         | 111 (28)     | 618 (27)             | 0.847 |
| Number of deaths  | 3 (1)        | 236 (10)             | <0.0001 |
| TB related deaths | 0 (0)        | 34 (1)               | <0.0001 |

INH: isoniazide; MDR: multidrug resistance; TB: tuberculosis.
* Except for the smear-positive pulmonary TB, the denominators for the percentages in the cases and TB controls columns are the total number of cases (n = 392) or TB controls (n = 2,316) respectively. For the smear-positive pulmonary TB, the denominators are the number of pulmonary TB cases (n = 205) or controls (n = 1,555).

Table 1
The distribution of women’s countries of origin varied (Figure 2). From 1993 to 2006, the largest proportion of migrant cases was constituted by African women (n = 202), especially from Somalia (686/202; 92%). The distribution according to geographical area of origin was similar among TB controls, but different from the pregnant/post-partum-controls, of whom 89% were Danes and of whom the majority of migrants was from other European countries (Table 1). Among migrants, the median time in Denmark since immigration was substantially shorter among TB cases (2.74 years; IQR: 1.52–4.64) compared with TB controls (3.98 years; IQR: 1.43–8.51). Generally, cases and TB controls were of significantly lower education, were less employed and had a lower yearly income than pregnant/post-partum controls (Table 1). In contrast to the cases and pregnant/post-partum controls, TB controls more frequently lived in crowded conditions (<5 persons in the household). The majority of cases had no noteworthy comorbidities comparable to pregnant/post-partum controls but were considerably different from the TB controls who had higher CCI (Table 1). Diabetes, HIV and hepatitis were more common among cases and TB controls than among pregnant/post-partum controls (Table 1).
Since the 1980s, the TB incidence has declined among native Danes whereas the proportion of migrants among all TB cases has steadily increased now constituting approximately two-thirds of cases [20]. In our study, we found an even higher proportion of migrants, accounting for 92% of cases. The majority were migrant women from Africa among whom 87% (199/228) were Somalis. In line with our findings, a study from the UK found TB during pregnancy limited to ethnic minority women, most commonly recent migrants [22]. Likewise, a study from the United States (US) found a higher proportion of ethnic minorities, such as Hispanic women, with TB during pregnancy [2]. In the 1990s, Denmark experienced a large arrival of migrants from Somalia due to civil war. This arrival is evident in the TB statistics (Figure 2). Therefore, variations in TB cases’ origin will also reflect the TB risk in pregnancy. The composition of migrants will change over time and be affected by wars, political conflicts and natural disasters that may force people to flee from their homelands. This diversity of migrants should be considered when planning control interventions addressing pregnant migrants.

In this study, few cases were employed, and a high proportion received cash benefits (59%). However, in line with publicly available data, female migrants from non-European countries are more frequently recipients of social welfare benefits than Danish women [23]. Though our case population was quite young (one-third below 25 years of age), the educational level was still remarkably low as was the income compared with the

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**Table 3**

Associations between tuberculosis and origin, socioeconomic status, and comorbidity among women diagnosed with tuberculosis while pregnant or in the post-partum period (cases) and pregnant/post-partum controls, Denmark, 1990–2018 (n = 6,906)

| Characteristic                        | Univariable logistic regression | Characteristic                        | Multivariable logistic regressiona |
|---------------------------------------|---------------------------------|---------------------------------------|----------------------------------|
| WHO region of origin (n = 6,904)      |                                 | WHO region of origin (n = 6,904)       |                                  |
| OR 95% CI p< 0.0001                   |                                 | OR 95% CI p< 0.0001                   |                                  |
| European Region Ref NA Ref          |                                 | European Region Ref NA Ref           |                                  |
| Region of the Americas 7.82 1.02–61.3 0.05 | Region of the Americas 7.14 0.88–58.1 0.0761 |                                   |                                  |
| African Region 396 270–581 < 0.0001   | African Region 187 125–281 < 0.0001 |                                 |                                  |
| Eastern Mediterranean Region 26.5 17.7–39.6 < 0.0001 | Eastern Mediterranean Region 11.8 7.56–18.4 < 0.0001 |                                   |                                  |
| South-East Asian Region 72.1 41.1–126 < 0.0001 | South-East Asian Region 50.2 27.7–91.0 < 0.0001 |                                   |                                  |
| Western Pacific Region 49.5 29.5–83.1 < 0.0001 | Western Pacific Region 36.9 20.9–62.3 < 0.0001 |                                   |                                  |
| Number of persons in household (n=6,904) | < 0.0001                       | Number of persons in household (n=6,904) | 0.0009                           |
| 1 Ref NA Ref |                                 | 1–4 Ref NA Ref |                                 |
| 2–3 4.69 1.72–12.8 0.0025 | 1–4 1.94 1.31–2.84 0.0009 |                                 |                                  |
| 4–5 8.22 3.03–22.3 < 0.0001 |                                 | ≥ 5 1.94 1.31–2.84 0.0009 |                                 |
| > 5 48.2 17.6–131 < 0.0001 |                                 | ≥ 5 1.94 1.31–2.84 0.0009 |                                 |
| Educational level (n=6,720) | < 0.0001                       | Educational level (n=6,720) | ND                               |
| Elementary school Ref NA Ref |                                 | Elementary school ND ND ND |                                 |
| High school 0.70 0.52–0.93 0.0153 | High school ND ND ND |                                 |                                  |
| Short higher 0.58 0.43–0.77 < 0.0001 | Short higher ND ND ND |                                 |                                  |
| University degree 0.37 0.25–0.56 < 0.0001 | University degree ND ND ND |                                 |                                  |
| Employment status < 0.0001 |                                 | Employment status 0.0151 |                                 |
| Employed Ref NA Ref |                                 | Employed Ref NA Ref |                                 |
| Not-employed 16.1 11.7–22.2 < 0.0001 | Not employed 2.04 1.15–3.63 0.0151 |                                 |                                  |
| Yearly income (EUR) < 0.0001 |                                 | Yearly income (EUR) 0.0005 |                                 |
| < 15,000 Ref NA Ref |                                 | < 15,000 Ref NA Ref |                                 |
| ≥ 15,000 0.05 0.03–0.07 < 0.0001 | ≥ 15,000 0.31 0.16–0.59 0.0005 |                                 |                                  |
| Charlson comorbidity index 0.2929 |                                 | Charlson comorbidity index 0.9177 |                                 |
| 0 Ref NA Ref |                                 | 0 Ref NA Ref |                                 |
| ≥ 1 0.86 0.64–1.14 0.2929 | ≥ 1 0.98 0.64–1.50 0.9177 |                                 |                                  |

CI: confidence interval; NA: not applicable; ND: not determined; OR: odds ratio; Ref: reference; WHO: World Health Organization.

In case of missing data for a variable, the number of cases with known information is indicated in parentheses.

a All the listed variables, except education were adjusted for in the final multivariable model.

b Wald test.

c The variable ‘persons in household’ was simplified in the multivariable model to express crowding (≥ 5 persons in household) vs no crowding (<5).
The category is based on the geographical area of origin.

Wald test.

In the final multivariable model there has been adjusted for all can be misinterpreted as pregnancy-related [2,23,25]. Sweden [11] who observed the highest incidences in pregnancy [12,24,25], but also because TB symptoms more conservative approach to investigations during birth rather than during pregnancy could be due to a associated TB cases are diagnosed after they give 8 www.eurosurveillance.org

In this study, most TB cases were diagnosed during pregnancy, in contrast to findings from the UK [12] and Sweden [11] who observed the highest incidences in the post-partum period (cases) and tuberculosis controls, Denmark, 1990–2018 (n = 2,708)

Table 4

Associations between severe tuberculosis and origin, socioeconomic status, and comorbidity among women diagnosed with tuberculosis while pregnant or in the post-partum period (cases) and tuberculosis controls, Denmark, 1990–2018 (n = 2,708)

| Characteristic | Multivariable logistic regression a |  |  |
|---------------|-----------------------------------|---|---|
|               | OR                                 | 95% CI | p b |
| Category      |                                    |   |   |
| Danes         | 1                                  | Ref | 0.9689 |
| Migrants      | 0.98                               | 0.34–2.42 | |
| Charlson comorbidity index | |   |   |
| 0             | 1                                  | Ref | 0.2688 |
| ≥1            | 0.68                               | 0.34–1.34 | |
| Employment status | |   |   |
| Employed      | 1                                  | Ref | 0.8183 |
| Not-employed  | 0.87                               | 0.28–2.75 | |
| Yearly income (EUR) | |   |   |
| ≤15,000       | 1                                  | Ref | 0.1792 |
| ≥15,000       | 0.34                               | 0.07–1.63 | |

a In the final multivariable model there has been adjusted for all the listed variables.
b Wald test.
c The category is based on the geographical area of origin.

pregnant/post-partum controls, reflecting a vulnerable group in the society.

In this study, most TB cases were diagnosed during pregnancy, in contrast to findings from the UK [12] and Sweden [11] who observed the highest incidences in the post-partum period. The fact that many pregnancy-associated TB cases are diagnosed after they give birth rather than during pregnancy could be due to a more conservative approach to investigations during pregnancy [12,24,25], but also because TB symptoms can be misinterpreted as pregnancy-related [2,23,25]. Diagnostic delay can potentially cause more severe disease manifestations. A study from the US found significantly higher maternal mortality among all women with TB during pregnancy relative to controls, attributed to delayed diagnosis and treatment [2]. In the current study however, we found no signs of more severe TB manifestations among cases compared with TB controls and, in addition, there was no increased maternal mortality among cases compared with controls.

Previous studies have demonstrated that in Europe, migrants from Africa and Asia have a higher risk of adverse pregnancy outcomes, though conflicting data exist [26-30]. In Denmark, the antenatal care programme is free to all women with legal residency [31] and it consists of consultations with a doctor and a midwife, antenatal and parent preparation classes, invitations to blood tests, and two ultrasound scans performed to provide early risk assessment and to test for congenital malformations [32]. This comprehensive programme could be an ideal opportunity to perform systematic TB screening in selected women at risk of TB. Testing for HIV and hepatitis is already part of the Danish standard antenatal programme [32]. In Sweden, the Public Health Agency recommends TB screening among pregnant women from high-incidence countries or with known exposure [33]. A recent study evaluated the yield of the new screening programme in Sweden [33], and interestingly, 22% of screened pregnant women from TB high-incidence countries were Interferon Gamma Release Assays (IGRA) positive and a high proportion completed preventive treatment [13], thereby substantially lowering the risk of later TB due to reactivation. Like Sweden, the Centers for Disease Prevention and Control (CDC) in the US recommends screening to women from TB high-incidence countries. There may be undiagnosed/never reported cases of TB among pregnant migrants e.g. undocumented migrants not having a CPR number, which would result in underestimating the TB risk among pregnant migrants, however we consider this to not affect the final risk estimates and therefore to not change our main findings and conclusion. By including all possible TB cases and all possible pregnancies in the unique Danish register-data-system and by having population controls reflecting the origin and SES distribution in Denmark, we believe that our data are generalisable. Although we adjusted for potential confounders in the regression analyses, there remains a risk of residual confounding from unmeasured or not included factors such as increased risk of exposure in certain environments or increased risk of reactivation of TBI due to risky behaviour e.g. homelessness and drug misuse, or other conditions not associated with

Our study has three major strengths: the nationwide design, long study period, and comprehensive nationwide registers with individually-linked data through the unique CPR number. We have minimised the risk of selection bias by including all cases of TB diagnosed when pregnant and in the post-partum period during the study. However, there are some limitations. The pregnant/post-partum controls were systematically included from a prior-selected control group containing all controls matched individually on sex and age to TB cases, therefore the controls were not entirely uncorrelated with the pregnant/post-partum TB cases (Figure 1). The risk of misclassified cases appearing among controls is very small in this study, because TB in Denmark is rare and TB during pregnancy even more rare. The vast majority of our cases in this study were migrants from TB high-incidence countries. There may be unreported cases of TB among pregnant migrants e.g. undocumented migrants not having a CPR number, which would result in underestimating the TB risk among pregnant migrants, however we consider this to not affect the final risk estimates and therefore to not change our main findings and conclusion. By including all possible TB cases and all possible pregnancies in the unique Danish register-data-system and by having population controls reflecting the origin and SES distribution in Denmark, we believe that our data are generalisable. Although we adjusted for potential confounders in the regression analyses, there remains a risk of residual confounding from unmeasured or not included factors such as increased risk of exposure in certain environments or increased risk of reactivation of TBI due to risky behaviour e.g. homelessness and drug misuse, or other conditions not associated with
pregnancy. Such residual confounding could lead to an overestimation of the pregnancy-related TB risk. The retrospective observational design relies on existing register information leaving the possibility of information bias. The data on education and employment are not complete as many migrants arrived after finishing school in their home countries or arrived recently and were not yet employed. Furthermore, cases were relatively young and could have achieved higher education, employment and income later in life. Nonetheless, this would apply to both cases and controls and should not affect the final estimates. We did not review medical files which might have provided additional information e.g. on possible diagnostic delays and/or clinical symptoms. Thus, the severity of TB discussed in this study is based on proxies for severe disease manifestations.

Conclusions

Tuberculosis among pregnant and post-partum women primarily occurs among migrants during the first 3 years after arrival to Denmark. Pregnant women with TB constitute a vulnerable group as TB may cause adverse events among mothers and their newborn children. Therefore, we recommend an increased focus on this population and suggest to evaluate targeted TBI and active TB screening of selected at-risk pregnant women, which may prevent future cases.

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Conflict of interest

None declared.

Authors’ contributions

ACN, CHS, AK, TL and ABA contributed to the study design and formulated the research question. ACN and AN contributed to data management. ACN and CTE performed the statistical analysis. ACN, CHS, AN, CTE, PE, TL, AK, ABA all contributed to interpreting data. ACN drafted the manuscript, and all authors have revised it critically. All authors have read and approved the final manuscript for publication.

References

1. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. Lancet Glob Health. 2014;2(12):e710-6. https://doi.org/10.1016/S2214-109X(14)70330-4 PMID: 25433626
2. El-Messidi A, Cruzoj-Sulman N, Spence AR, Abenhaim HA. Medical and obstetric outcomes among pregnant women with tuberculosis: a population-based study of 7.8 million births. Am J Obstet Gynecol. 2016;215(6):797.e4-6. https://doi.org/10.1016/j.ajog.2016.08.009 PMID: 27330490
3. Sobhy S, Babiker Z, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. BJOG. 2017;124(5):727-33. https://doi.org/10.1111/1471-0528.14408 PMID: 27862893
4. Dennis EM, Hao Y, Tamambang M, Roshan TN, Gatlin KJ, Bghigh H, et al. Tuberculosis during pregnancy in the United States: Racial/ethnic disparities in pregnancy and postpartum and in hospital death. PLoS One. 2018;13(3):e0194836. https://doi.org/10.1371/journal.pone.0194836 PMID: 29579086
5. Snow KJ, Bekker A, Huang GK, Graham SM. Tuberculosis in pregnant women and neonates: A meta-review of current evidence. Paediatr Respir Rev. 2020;36:27-32. https://doi.org/10.1016/j.prrv.2020.02.001 PMID: 32144052 PMID: 32144052
6. Marais BI, Lönnroth K, Lawn SD, Migliori GB, Mwaba P, Glaziou P, et al. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. Lancet Infect Dis. 2013;13(6):436-48. https://doi.org/10.1016/S1473-3099(13)70050-5 PMID: 23531392
7. Wolf B, Krasselt M, de Faiollos J, van Braun A, Stepan H. Tuberculosis in Pregnancy - a Summary. Geburtshilfe Frauenheilkd. 2019;79(4):338-85. https://doi.org/10.1055/a-0774-7924 PMID: 3100880
8. Yip L, McCluskey J, Sinclair R. Immunological aspects of pregnancy. Clin Dermatol. 2006;24(2):84-7. https://doi.org/10.1016/j.clindermatol.2005.10.022 PMID: 16487878
9. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav. 2012;62(3):263-71. https://doi.org/10.1016/j.yhbeh.2012.02.023 PMID: 2240614
10. Kraus TA, Engel SM, Sperling RS, Kellerman L, Lo Y, Wallenstein S, et al. Characterizing the tuberculosis immune phenotype: results of the viral immunity and pregnancy (VIP) study. J Clin Immunol. 2012;32(2):300-11. https://doi.org/10.1007/s10875-011-9627-2 PMID: 22198680
11. Jonsson J, Kühmann-Berenzon S, Berggren I, Bruchfeld M, Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis during pregnancy in the UK. BJOG. 2017;124(12):e675-6. https://doi.org/10.1111/1471-0528.14408 PMID: 27862893
12. World Health Organization (WHO). Definitions and reporting framework for tuberculosis–2013 revision. Geneva: WHO; Dec 2013. Available from: https://www.who.int/tb/publications/global_report/2013/en/
13. European Centre for Disease Prevention and Control (ECDC). Tuberculosis Surveillance report. Stockholm: ECDC; 2018.
14. European Centre for Disease Prevention and Control (ECDC). Public health guidance on screening and vaccination for infectious diseases in newly arrived migrants within the EU/EEA. Stockholm: ECDC; 2018.
15. Kunz H, Burman M, Arnesen TM, Fiebig L, Hergens MP, Kalkouni O, et al. Tuberculosis and latent tuberculosis screening of all migrants in Europe: comparative analysis of policies, surveillance systems and results. Int J Tuberc Lung Dis. 2017;21(8):840-51. https://doi.org/10.5588/ijtld.17.0036 PMID: 28786791
16. Koch A, Bjarn-Mortensen K, Johansen MB, Homae AS, Homea P. Infectious diseases with public health impact in Greenland. [Infektionssygdomme med betydning for folkesundheden i Grønland]. Ugeskr Laeger. 2020;182(4):V12906889. PMID: 32515334
17. World Health Organization (WHO). Definitions and reporting framework for tuberculosis–2013 revision. Geneva: WHO; Dec 2014. 1-47.
18. Knight M, Kurinczuk JJ, Nelson-Piercy C, Spark P, Brocklehurst P, UKOSS. Tuberculosis in pregnancy in the UK. BJOG.
23. Statistics Denmark. Migrants in Denmark 2010. [Indvandrere i Danmark 2010]. 2010. Danish.

24. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis. 2012;55(1):1532-49. https://doi.org/10.1093/cid/cis732 PMID: 22942202

25. Bothamley GH, Ehlers C, Salonka I, Skrahina A, Orcau A, Codecasa LR, et al. Pregnancy in patients with tuberculosis: a TBNET cross-sectional survey. BMC Pregnancy Childbirth. 2016;16(1):304. https://doi.org/10.1186/s12888-016-1096-4 PMID: 27729022

26. Gissler M, Alexander S, MacFarlane A, Small R, Stray-Pedersen B, Zeitlin J, et al., for the ROAM collaboration (Reprodu. Stillbirths and infant deaths among migrants in industrialized countries. Acta Obstet Gynecol Scand. 2009;88(2):134-48. https://doi.org/10.1080/00016340802603905 PMID: 19096947

27. Gagnon AJ, Zimbeck M, Zeitlin J, Alexander S, Blondel B, Buitendijk S, et al., ROAM Collaboration. Migration to western industrialised countries and perinatal health: a systematic review. Soc Sci Med. 2009;69(6):934-46. https://doi.org/10.1016/j.socscimed.2009.06.027 PMID: 19664869

28. Villadsen SF, Mortensen LH, Andersen AMN. Care during pregnancy and childbirth for migrant women: How do we advance? Development of intervention studies--the case of the MAMAACT intervention in Denmark. Best Pract Res Clin Obstet Gynaecol. 2016;32:100-12. https://doi.org/10.1016/j.bpqogyn.2015.08.013 PMID: 26472711

29. Villadsen SF, Mortensen LH, Andersen AMN. Ethnic disparity in stillbirth and infant mortality in Denmark 1981-2003. J Epidemiol Community Health. 2009;63(2):106-12. https://doi.org/10.1136/jech.2008.078741 PMID: 18930979

30. Pedersen GS, Mortensen LH, Gerster M, Rich-Edwards J, Andersen AMN. Preterm birth and birthweight-for-gestational age among immigrant women in Denmark 1978-2007: a nationwide registry study. Paediatr Perinat Epidemiol. 2012;26(6):534-42. https://doi.org/10.1111/ppe.12010 PMID: 23061689

31. The Danish Ministry of Health. Sundhedsloven (The Health Law) LBK nr 903. Sundhedsloven 2019.

32. The Danish Health Authority [Sundhedsstyrelsen]. New in Denmark–pregnancy and birth. Sundhedsstyrelsen; 2016.

33. The Public Health Agency of Sweden [Folkhälsomyndigheten]. Recommendations on preventive measures against latent tuberculosis. [Rommendationer för preventiva insatser mot tuberkulos–hälsokontroll, smittspårning, behandling av latent infektion och vaccination.]. Folkhälsomyndigheten; 2020.

34. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in Pregnancy. Obstet Gynecol. 2020;135(6):1444-53. https://doi.org/10.1097/AOG.0000000000003894 PMID: 32459437

35. Langholz Kristensen K, Lillebaek T, Holm Petersen J, Hargreaves S, Nellums LB, Friedland JS, et al. Tuberculosis incidence among migrants according to migrant status: a cohort study, Denmark, 1993 to 2015. Euro Surveill. 2019;24(44). https://doi.org/10.2807/1560-7917.ES.2019.24.44.1900238 PMID: 31690363

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