Appendix 1 Classification of immunosuppressive risk factors for tuberculosis disease

ATC codes classified according to: WHO Collaborating Centre for Drug Statistics Methodology, ATC classification index with DDDs 2016. Oslo 2015.
ICD-10 codes classified according to: Directorate of e-health Norway, International Classification of Diseases 10th revision. 2017

Marker of risk		ICD-10/[NCMP]-codes [I]	AND/OR	ATC-codes [II]
Underlying disease, any		Summary of lines 1-15		Summary of lines 1-15
1	HIV infection	B20-B24, O987, R75, Z21	OR	J05AR
2	Diabetes	E10-E14 O24	OR AND	A10 A10
3	Silicosis	J65		
4	Chronic renal disease with or without haemodialysis	N01, N03, N04, N11, N18, [KAGD40, Z992*, JAGD30, JAGD31, JAGD50]	OR	V03AE02, V03AE03
5	Malignant neoplasms, any	C00-C97		
6	Solid organ transplant	T86.0-T86.4, T86.8, T86.9, Z94		
	Diseases relevant for DMARDs treatment, any [III]	Summary of lines 7-12		
7	Inflammatory polyarthropathies	M05-M13		
8	Systemic connective tissue disorders	M30-M35		
9	Spondylopathies	M45-M46		
10	Papulosquamous disorders	L40-L41		
11	Non-infective enteritis and colitis grouped	K50-K51		
12	Multiple sclerosis	G35		
13	Malnutrition	E40-E46		
14	Dependence syndrome, alcohol	F10.2	OR	N07BB
15	Dependence syndrome, opioids	F11.2	OR	N07BC01/02, N07BC51
Iatrogenic immunosuppression, any		Summary of lines 16-22	OR	Summary of lines 16-22
16	Antineoplastic agents	[L01XC02]	OR	L01
17	Selective immunosuppressants	[L04AA24]	OR	L04AA
18	TNF-alpha inhibitors	[L04AB01/02/04/05/06]	OR	L04AB
19	Interleukin inhibitors	[L04AC03/05/07]	OR	L04AC
20	Calcineurin inhibitors			L04AD
21	Other immunosuppressants			L04AX
22	Long term steroid treatments			H02AB DDD > 15mg > 1 month

[I] Hospital discharge data from the Norwegian Patient Registry (NPR), ICD-10: International Classification of Diseases 10th revision, NCMP: the Norwegian Classification of Medical Procedures. Underlying diseases included registrations prior to or at the time of administration of the QuantiFERON®TB-Gold

[II] Outpatient prescriptions data from the Norwegian Prescription Database (NORPD): ATC: Anatomical Therapeutic Chemical Classification System. Iatrogenic immunosuppression included drugs if there was at least one prescription within the last six months prior to QuantiFERON®TB-Gold

[III] DMARDs, Disease Modifying Anti-Rheumatic Drugs

Appendix 2, Detailed overview of statistical analyses of the main exposure and outcome

The main exposure was interferon-gamma (IFN-γ) levels in IU/ml reported as recommended by the manufacturer. Since risk of tuberculosis may change over time, and some individuals have more than one QFT®-test, we applied time-dependent Cox regression model to examine associations between the main outcome and the main exposure. This involved constructing a row of data for each QFT®, from the start of the interval (date of sampling) until the end of the interval (event, censoring or date of sampling for a subsequent test). Covariate values are those that apply over that interval. Using time-varying explanatory variables is more robust than selecting exposures from a single time point as it utilizes all available data.

Splines and categorization of IFN-γ levels

We had a priori information that the association between incident TB and IFN-γ levels in IU/ml was non-linear. Three laboratories only reported continuous IFN-γ levels until 10 IU/ml, and then reported "≥ 10 IU/ml" for the remaining. We therefore decided to model the continuous data using restricted cubic splines, which would give us insight into appropriate categorizations of the data and allowing usage of all the available results. Only tests with IFN-γ levels below 9.99 IU/ml were included in the spline models. We ran two regressions (including origin, age and identified medical risk factors as adjustment variables), one with knots at 0.35, 3, and 6 IU/ml, and the other with knots at 0.35, 0.7, 2.0, 4.0, 6.0 and 8.0 IU/ml. The lowest knot values (0.35, 0.7 and 1.00 IU/ml) were selected based on clinical interest, and the remaining on equal spacing. Both regressions supported the categorization of IFN-γ levels as negative at < 0.35 (according to manufacturer's cut-off), low positive at 0.35 to <1.0 IU/ml, medium positive at 1.0 to < 4.0 IU/ml, and high positive at $\geq$ 4.0 IU/ml. We used these categories in all further analyses.

Effect modification and interaction terms

To investigate if the association between IFN-γ levels IU/ml and incident TB disease was modified by origin, age or identified medical risk factor, we ran the following models:

(i) baseline model: incident TB = (categorized IFN-γ levels) + (age) + (origin) + (medical risk factor),

(ii) modified by origin model: incident TB = (categorized IFN-γ levels) + (age) + (origin) + (medical risk factor) + (categorized IFN-γ levels)*(origin), and

(iii) modified by age model: incident TB = (categorized IFN-γ levels) + (age) + (origin) + (medical risk factor) + (categorized IFN-γ levels)*(age).

(iv) modified by medical risk factors model: incident TB = (categorized IFN-γ levels) + (age) + (origin) + (medical risk factor) + (categorized IFN-γ levels)*(medical risk factor).

We then performed likelihood ratio tests comparing the various models to the "baseline model". We found no statistically significant effect of age, origin or identified medical risk factors on the IFN-γ levels (IU/ml) and these co-variates were included in the model.

Numbers needed to treat (NNT)

Number needed to treat for latent tuberculosis infection to prevent one case with incident tuberculosis disease was calculated by estimating the difference in risk of incident TB among individuals who did not and those who did receive LTBI treatment. NNT=1/(incident TB/number of individuals not receiving LTBI treatment –incident TB/individuals receiving LTBI treatment)

Appendix 3, Sensitivity analysis – definition of incident tuberculosis disease

In this sensitivity analysis, we defined a case as incident tuberculosis (TB) if date of sample collection for TB diagnosis was ***more than six months* after the QFT® administration**, as compared to *more than three months* after QFT® administration in the main analyses

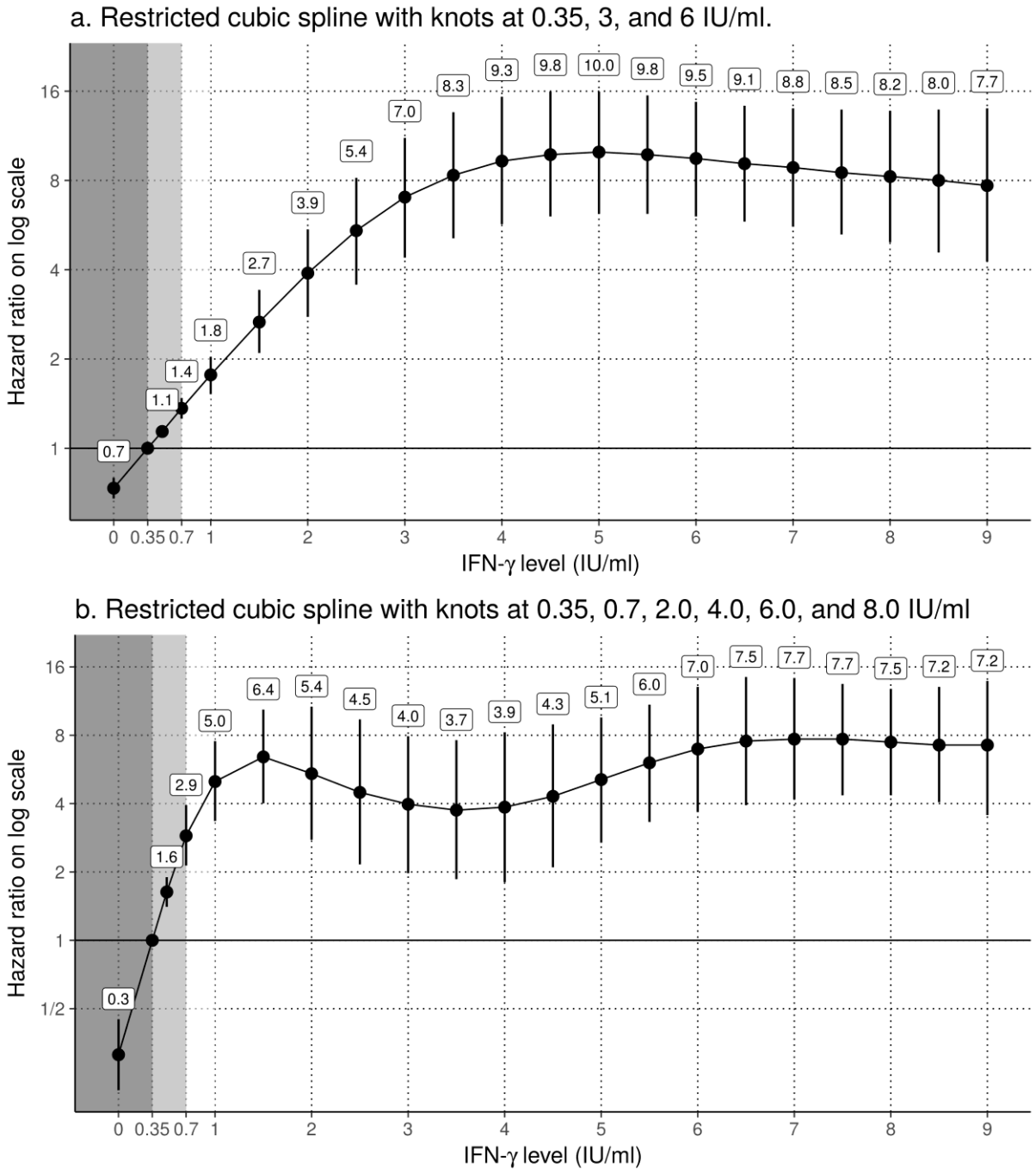
Hazard ratios for incident tuberculosis disease (n=170) by IFN-γ level, origin, age and medical risk-factors, n=43923, by time-dependent Cox regression*

Covariates	TB events	HZ	*p*	95% CI
IFN-γ level IU/ml [a]				
IFN-γ < 0.35	20	0.15	< 0.001	0.07-0.36
IFN-γ >=0.35 to < 1.0	9	1 (ref)		
IFN-γ >= 1.0 to < 4.0	30	2.28	0.030	1.08-4.82
IFN-γ >= 4.0	111	4.30	< 0.001	2.16-8.46
Origin				
Foreign-born	156	1 (ref)		
Norwegian-born	14	0.40	0.004	0.21-0.74
Age-group				
Age ≥ 35 yrs	117	1 (ref)		
Age < 35 yrs	53	1.65	0.003	1.19-2.30
Any medical risk factor [b]				
No risk factors	150	1 (ref)		
At least one risk factor	20	1.42	0.193	0.84-2.39

TB events, TB diagnosed more than 6 months after the QFT® administration; Yrs, sum of person years follow-time after QFT®; HZ, hazard ratio

[b] *Information about medical risk factors is based on ICD10/NCMP codes from Norwegian Patient Registry and ATC-codes from Norwegian Prescription Registry.*

Appendix 4 Hazard ratios for incident **culture confirmed** tuberculosis (n=150) by IFN-γ level compared with the reference level of 0.35 IU/ml (*n* = 41,431 individuals).



Only results with IFN-γ < 10.0 IU/ml were included in the models. Individuals with TB not confirmed by culture (=102) were excluded from the analyses.

Grey shaded areas represent negative (<0.35 IU/ml), and low positive (> 0.35 to < 0.7 IU/ml, and >0.7 to <1.0 IU/ml) IFN-γ level