Inadequate Diet Is Associated with Acquiring *Mycobacterium tuberculosis* Infection in an Inuit Community

A Case–Control Study

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Abstract

Background: Tuberculosis predominantly affects socioeconomically disadvantaged communities. The extent to which specific dietary and lifestyle factors contribute to tuberculosis susceptibility has not been established.

Methods: A total of 200 residents of a village in Northern Quebec were investigated during a tuberculosis outbreak and identified to have active tuberculosis, latent tuberculosis infection, or neither. Participants completed questionnaires about their intake of food from traditional and commercial sources, and provided blood samples. Adults were asked about recent smoking and drug and alcohol intake. Nutritional adequacy was evaluated with reference to North American standards. Multiple dietary, lifestyle, and housing factors were combined in a logistic regression model evaluating the contributions of each to disease and infection.

Findings: After adjusting for potential confounding, new infection was associated with inadequate intake of fruit and vegetables (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.03–4.3), carbohydrates (OR, 4.4; 95% CI, 1.2–16.3), and certain vitamins and minerals. A multivariable model, combining nutrition, housing, and lifestyle factors, found associations between new infection and inadequate fruit and vegetable intake (OR, 2.3; 95% CI, 1.0–5.1), living in the same house as a person with smear-positive tuberculosis (OR, 14.7; 95% CI, 1.6–137.3), and visiting a community gathering house (OR, 3.7; 95% CI, 1.7–8.3). Current smoking was associated with new infection (OR, 9.4; 95% CI, 1.2–72) among adults completing a detailed lifestyle survey.

Interpretation: Inadequate nutrition was associated with increased susceptibility to infection, but not active tuberculosis. Interventions addressed at improving nutrition may reduce susceptibility to infection in settings where access to healthy foods is limited.

Keywords: tuberculosis; nutritional status; latent tuberculosis; disease outbreaks; nutrition

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Tuberculosis is an airborne infectious disease that affected an estimated 9 million people in 2014 (1). This enormous burden of disease falls disproportionately on socioeconomically disadvantaged communities where nutritional deficiency is common (2). Poor nutrition and tuberculosis are both associated with poverty, economic instability, and food insecurity (3–5). Observational studies have found associations between active tuberculosis and diet (6), nutritional status (7, 8), and other socioeconomic factors, such as housing, as well as lifestyle factors, such as cigarette smoking and alcohol and other substance use (9–11). However, crowded housing, cigarette smoking, or limited access to health care are often closely correlated, making it difficult to determine the most important of these risk factors, and few studies have attempted to measure many of these potential factors at once. The relationship between these factors and *Mycobacterium tuberculosis* infection, the antecedent of active tuberculosis, has not yet been established.

Indigenous communities in many high-income countries have substantially higher rates of tuberculosis than the nonindigenous population (12), and rates of tuberculosis are particularly high among the Inuit in the Canadian Arctic regions (13). Although socioeconomic factors are thought to be important contributors, the reasons for this remain unclear, making it difficult to target interventions to reduce this disease burden. This study was conducted in an isolated Inuit community in northern Quebec after a massive outbreak, in which 10% of the entire community was treated for active tuberculosis over a 1-year period, and 28% of people with evidence of new infection developed disease. In light of the extraordinary burden of disease in the context of an indigenous community, we studied the socioeconomic factors associated with latent tuberculosis infection and active disease. We aimed to determine the relationship between dietary and lifestyle factors and the development of active disease, and infection, during the outbreak.

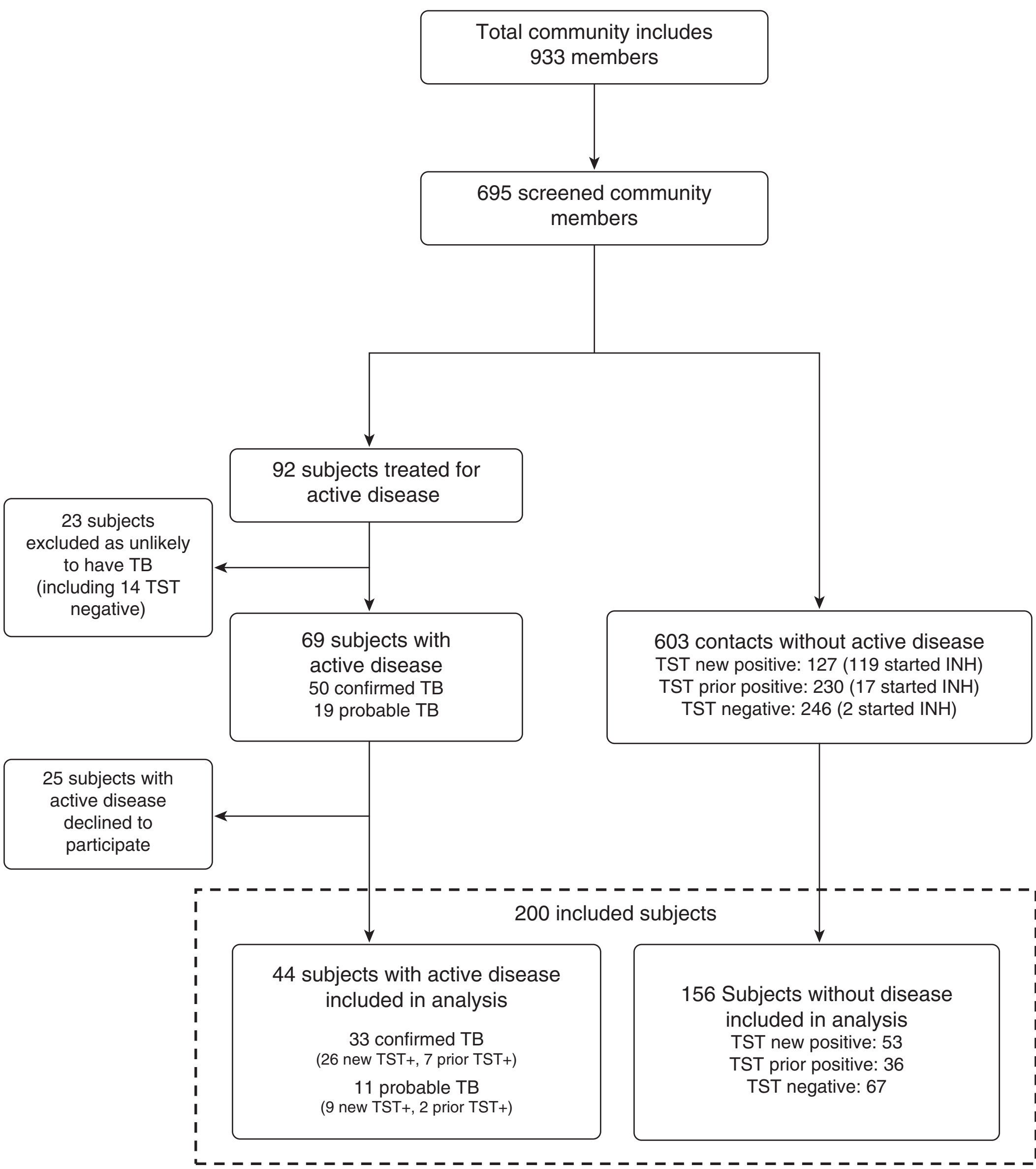

Figure 1. Summary of selection of study participants. 200 participants included in either case-control study 1 (newly infected versus uninfected) or case control-study 2 (disease versus no disease among all infected). The number of subjects included in each comparison is shown in Figure 2. INH = 9-month course of isoniazid preventive therapy; TB = tuberculosis; TST = tuberculin skin test. Screening was comprised of a chest radiograph, clinical assessment, and tuberculin skin test to determine disease and infection status.

Methods

Study Setting

This study was conducted after a tuberculosis outbreak investigation at the village of K. in the Nunavik region of northern Quebec (Canada) between November 2011 and November 2012 (Figure 1). Index patients with active tuberculosis were identified through passive case finding and contact investigation. Of a total village population of 933 people, 92 (10%) were diagnosed and treated for tuberculosis, including 50 (5%) with bacteriologically confirmed disease; 695 community members were screened, of whom 162 (23%) were newly infected. Disease incidence was higher among individuals with new infection (28%) than those with prior infection (6.5%). Migration in and out of the community is limited, owing to its geographical isolation. The socioeconomic status of the community was lower than that of the province (14).

At the time of the outbreak, all residents of the village who were identified as contacts of a person with active tuberculosis were assessed, including clinical history, physical examination and plain chest radiograph. Tuberculin skin testing was performed on all contacts unless there was a documented prior infection (as defined subsequently here). If the initial tuberculin skin test result was negative, a second tuberculin skin test was performed 8 weeks after the exposure. Contacts with radiographic or clinical suspicion of active tuberculosis provided three spontaneous sputum samples or underwent sputum induction, followed by nucleic acid amplification testing and culture, if positive.

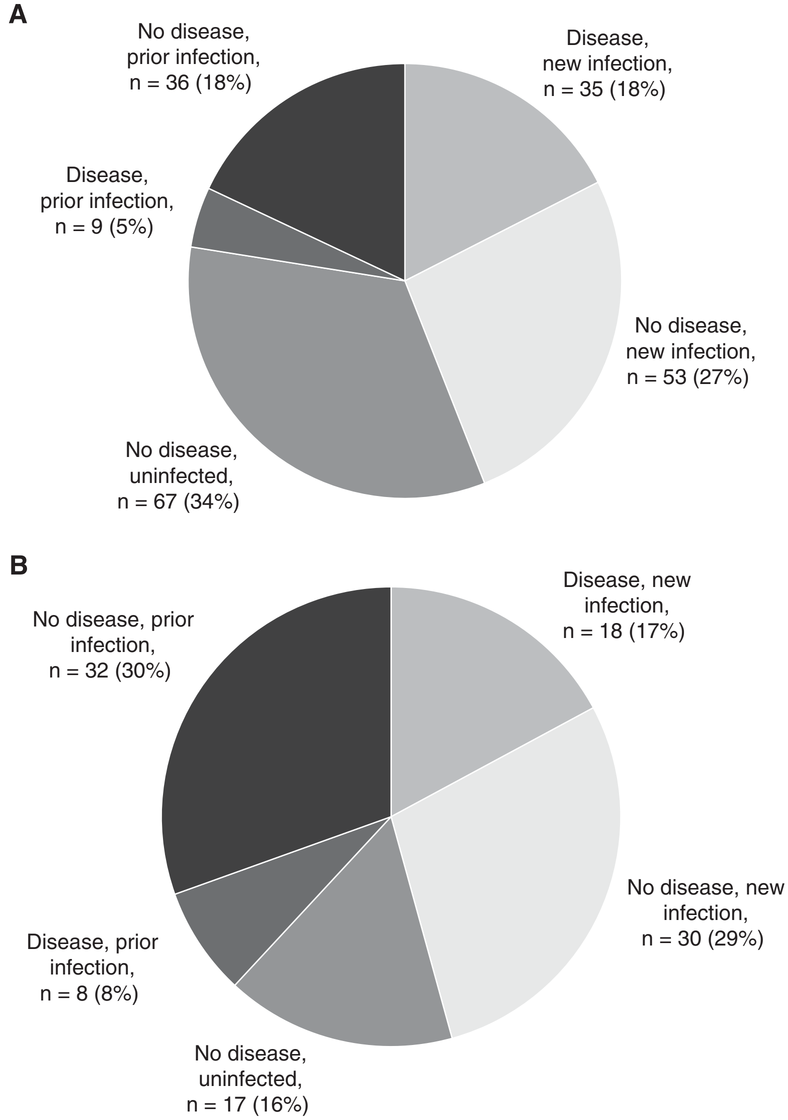

Figure 2. Summary of participants by infection and disease status. (*A*) Infection and disease status of 200 nutrition survey participants. (*B*) Infection and disease status of 105 lifestyle survey participants.

Study Design and Participants

We conducted two overlapping case–control studies, nested within the 695 community members who, between November 2011 and November 2012, resided in the village and were either diagnosed with confirmed or probable active disease, or were identified as contacts of someone with confirmed or probable disease and had at least one TST performed during this period, or had a documented prior positive TST (*see* Figure 2).

For our first objective (case–control study 1), we compared participants with new infection with *M. tuberculosis* with or without disease (cases) to an equal number of contacts who remained uninfected (control subjects). This comparison excluded subjects with prior infection, as infection (new or repeated) cannot be identified with a prior positive tuberculin skin test.

For the second objective (case–control study 2), we compared participants with confirmed or probable disease (cases) to those with infection, but no disease (control subjects). We planned to recruit as many persons with confirmed or probable active tuberculosis as possible, and aimed to recruit twice as many persons without disease, but with latent tuberculosis infection, to serve as control subjects. The comparison of active disease versus no disease among infected subjects (case–control 2) was stratified by whether the infection was new or prior. Hence, the numbers of participants selected with new or prior infection without disease were proportionate to the numbers of participants with new or prior infection who developed active disease. Because of the small number of persons with active disease, we did not match cases or control subjects by any characteristic, but rather adjusted for any differences in multivariable analysis.

Definitions of New Infection with *M. tuberculosis* and Active Tuberculosis

A positive tuberculin skin test reaction was defined according to Canadian standards

(13). New infection with *M. tuberculosis* ("new infection") was defined as a positive tuberculin skin test of 5 mm or more performed as part of the outbreak investigation with no prior documented tuberculin skin test, or newly positive with a prior documented negative tuberculin skin test (termed "conversion"). A prior positive tuberculin skin test ("prior infection") was defined as a documented tuberculin skin test result of 10 mm or more in community health records before the start of the outbreak. Participants were considered uninfected if they had at least one documented negative tuberculin skin test during the outbreak, and no prior tuberculin skin test result, nor any evidence of active disease.

Confirmed tuberculosis ("confirmed disease") was defined as the presence of at least one positive culture for *M. tuberculosis.* Probable disease was defined as the presence of typical clinical and/or radiological features, including improvement with antituberculosis therapy, but without culture confirmation. This designation was made by two experienced chest physicians who independently reviewed all clinical information and serial chest radiographs in a blinded fashion.

Villagers treated for active tuberculosis that was neither microbiologically confirmed nor considered probable disease were excluded, as were residents whose sole contact was one of these cases.

Treatment of Active Disease and Latent Tuberculosis Infection

Subjects considered to have active tuberculosis were treated with standard combination therapy (13). Treating physicians offered isoniazid preventive therapy for infected contacts with no evidence of active tuberculosis (Figure 1).

Data Collection

Dietary intake was assessed using semiquantitative interviewer-administered food-frequency questionnaires, adapted from a validated questionnaire used in an earlier survey among indigenous communities in Nunavik (15). The expanded 108-item food frequency questionnaire asked how often respondents had consumed a portion of each food, on average, during the previous year. Nine possible responses ranged from "never" to "more than six times a day." Foods were classified as either commercially available ("store bought," 77 items) foods or traditional ("land," 31 items) foods. Consumption of traditional foods was evaluated for all four seasons, to reflect changes in seasonal availability. The prevalence of food insecurity was based on an abridged Household Food Security Survey Module questionnaire (16).

A second questionnaire asked about employment, personal income, and education level of participants. A third questionnaire, completed only by 105 adults, explored possible socioeconomic and lifestyle risk factors for tuberculosis, including consumption of tobacco, alcohol (including beer, wine, and spirits), and cannabis and other illicit drugs in the last month. Subjects of all ages answered the first two questionnaires, with parents of children under 12 years of age completing the questionnaires on their behalf. Interviews were conducted in English, French, or Inuktitut.

Analysis of Nutritional Intake from Food Frequency Questionnaire

The daily intake of each nutrient was calculated by multiplying portion size (g) by the frequency of consumption (per day) for each individual. Composition values of foods was derived from the U.S. National Nutrient Database for Standard Reference version 26 (17). For 12 of the 31 traditional foods that were not included in the database, a nutritionally equivalent food type was selected from the database.

To account for outlying results associated with overreporting of intake, the intake of nutrients of individuals with energy intake in the upper 5% of the group was truncated to the upper range of the 95th centile of the study population.

Food group, nutritional adequacy, and portion sizes were defined according to Canadian standards (18), with the exception of potatoes, which were classified in the "other" food group (19). The adequacy of the daily intake of each food item for each individual was determined with reference to North American reference standards, based upon age and sex, and assuming typical levels of activity (20–24). Calories from alcohol were not included in the calculations, as this information was available only for a subset of participants.

Blood was collected from participants, without fasting. Automated analyzers were used to measure hemoglobin, platelet count, iron, vitamin D, and zinc levels. Cotinine (the primary metabolite of nicotine), vitamin A, and vitamin E were tested using HPLC. Vitamin D was classified as normal, insufficient, or deficient according to standard criteria (25). A detailed evaluation of household exposure and the ventilation in individual dwellings was also performed, and is reported separately (26). Current smoking was defined as either a self-reported history of current smoking or a positive serum cotinine test (27).

Statistical Analysis

Overall median daily intake of specific nutrients and food groups (meat, milk,

Table 1. Comparison of participants and nonparticipants

Infection Status*	Total *n*	Age Group			Male Sex† *n* (%)
		0–14 yr *n* (%)	15–29 yr *n* (%)	⩾30 yr *n* (%)	
New infection‡					
Participants	88	30 (34.1%)	44 (50%)	14 (15.9%)	40 (45.5%)
Nonparticipants	100	32 (32.0%)	46 (46.0%)	22 (22.0%)	45 (60.8%)
Prior infection‡					
Participants	45	2 (4.4%)	16 (35.6%)	27 (60%)	22 (48.9%)
Nonparticipants	202	11 (5.4%)	46 (22.8%)	145 (71.8%)	98 (48.8%)
No infection‡					
Participants	67	45 (67.2%)	17 (25.4%)	5 (7.5%)	31 (46.3%)
Nonparticipants	193	117 (60.9%)	55 (28.6%)	20 (10.4%)	104 (54.2%)

*No significant differences were found between the characteristics of participants and nonparticipants in any subgroup ($P > 0.05$ for all comparisons, using Fisher's exact test).
†Sex of two nonparticipants was missing, and age of one nonparticipant in the "no infection" category.
‡Includes individuals with or without disease. All individuals with disease had a positive tuberculin skin test.

grain, and dairy) was calculated. Odds ratios for the effects of various nutrients on the outcome of interest were estimated using multivariate logistic regression.

Robust SEs were calculated. In analyses of active tuberculosis arising among those with infection, documented prior infection was included as a covariate in the multivariable analysis. Linearity of the continuous covariates in the model was assessed using univariable lowess smoothed logit. Initial covariates were considered for the model based upon a directed acyclic graph. Selection of separate multivariable models for infection and active disease was based upon an estimate of model fit using reverse covariate selection, with covariates left in the model if they contributed to an improvement (reduction) in the quasi-likelihood information criteria (28, 29).

To assess the goodness of fit, we performed residuals analysis, which indicated that model assumptions were valid. Collinearity between nutritional variables was assessed using contingency tables. As there was correlation between multiple dietary factors, we adjusted for adequacy of just one representative food group (fruit and vegetables) in the final multivariable analysis. The final combined multivariable model was compiled, including household, nutritional, lifestyle, and food security data. Covariates in the combined model for infection were age stratum, sex, dietary adequacy of fruit and vegetable intake, living with a person with smear-positive tuberculosis, and visiting a “gathering house” (a communal venue used for socializing). Covariates in the final model for active disease included age stratum, sex, personal income, smoking status, prior infection, fruit and vegetable intake, and household occupancy. An interaction term was included for household occupancy and living with a person with smear-positive tuberculosis. A hierarchical generalized estimating equation was used, with an independent correlation structure, to account for household clustering (Proc Genmod, SAS version 9.3; SAS Institute Inc., Cary, NC).

Missing values for age, sex, personal income, and smoking status (each missing in <5% of responses) were approximated using multiple imputation with a Markov chain Monte Carlo approach. We considered this analysis to be hypothesis generating (exploratory), so we did not account for multiple comparisons. Analyses were performed using SAS.

Ethical Approval

This study was approved by the Institutional Review Board of McGill University, the Nunavik Health and Nutrition Committee, and the mayor and municipal council of the village.

Results

Demographics of Recruited Subjects

In total, 200 participants were studied, of whom 44 subjects had active disease (Figure 1). All of these had documented new or prior infection, and none of were human immunodeficiency virus (HIV) coinfected; 88 subjects were newly infected, 45 had prior documented

Table 2. Total daily nutrient intake and adequacy of intake among study participants

Food Group or Nutrient	Daily Reported Intake Median (IQR)	Respondents with an Inadequate Intake (*Total n* = *200*) *n* (%)
Food category		
Dairy, serves	1.6 (0.7–2.9)	140 (70.4)
Grain, serves	3.4 (2.2–4.9)	166 (83.4)
Meat or equivalent, serves*	4.1 (2.4–7.1)	39 (19.6)
Fruit and vegetables, serves†	7.0 (3.6–9.8)	98 (49.2)
Beverages		
Sugar sweetened beverages, serves‡	1.1 (0.1–2.6)	na
Sweet drinks, serves§	3.3 (1.3–6.1)	na
Nutrient		
Energy, kcal	2,498 (1,611–3,724)	59 (29.6)
Protein, g	95 (60–146)	20 (10.1)
Carbohydrates, g	320 (205–514)	21 (10.6)
Dietary fiber, g	18 (12–28)	156 (78.4)
Vitamin A, RAE	635 (365–964)	99 (49.7)
Vitamin B12, mcg	12 (6–24)	6 (3.0)
Vitamin D, IU	308 (180–697)	58 (29.1)
Vitamin C, mg	163 (90–295)	32 (16.1)
Thiamin, mg	2 (1–3)	37 (18.6)
Riboflavin, mg	2 (2–3)	22 (11.1)
Niacin, mg	31 (18–45)	26 (13.1)
Folate, mcg	379 (231–542)	80 (40.2)
Vitamin B6, mg	2 (1–4)	27 (13.6)
Calcium, mg	825 (537–1124)	141 (70.9)
Magnesium, mg	302 (203–439)	86 (43.2)
Phosphorous, mg	1,538 (988–2,198)	33 (16.6)
Iron, mg	22 (14–32)	42 (21.0)
Zinc, mg	11 (7–19)	58 (29.1)
Selenium, μg	123 (76–190)	18 (9.0)
Sodium, mg	1,636 (1,012–2,455)	84 (42.2)
Caffeine, mg	138 (60–242)	na
Lipids, g	83 (51–129)	14 (7.0)
Polyunsaturated fats, g	15 (9–23)	na
ALA, 18–3 g	0 (0–0)	na
EPA, 20–5 g	0.20 (0.1–1.0)	na
DHA, 22–6 g	0.40 (0.1–1.1)	na
Linoleic acid, g	6 (4–10)	na
CLA, g	0 (0–0)	na
Trans fats, g	0.4 (0.3–0.6)	na

Definition of abbreviations: ALA = α-linolenic acid; CLA = conjugated linoleic acid; DHA = docosahexaenoicacid; EPA = eicosapentaenoicacid; IQR = interquartile range; na = not applicable, where no dietary minimum level is applicable.

Daily intake calculated from a food frequency questionnaire.

*Includes meat, fish, and other meat equivalents.

†Excluded potatoes.

‡Sugar sweetened beverages include carbonated drinks.

§Sweetened drinks include carbonated drinks and sweetened or unsweetened fruit drinks.

infection, and 67 were uninfected (Figure 2). Survey participants did not differ significantly from nonparticipants ($P > 0.05$ for all comparisons, shown in Table 1).

Relationship between Diet and Infection with *M. tuberculosis* or Active Tuberculosis

Table 2 shows the median daily nutrient intake and the proportion of subjects with inadequate intake of each nutrient and food group. Only 11% of total daily energy intake was derived from traditional sources ("land" food; *see* Figure E1 in the online supplement).

Study participants with new infection (in case–control study 1) were more likely to report an inadequate intake of fruit and vegetables (Table 3). They were also more likely to report an inadequate intake of carbohydrates, vitamin A, thiamin, niacin, folate, magnesium, iron, and selenium. There was no association between active disease (in case–control study 2) and the reported dietary intake of diet groupings, or individual nutrients after adjustment for age, sex, personal income, smoking status, and prior infection (Table 4).

Food insecurity was reported by 76 of 105 (72.4%) adults and 149 of 197 (75.6%) subjects in the whole study population (Table E1). However, food insecurity was not associated with infection or active disease (results not shown).

Results of participants' blood tests, stratified by age, are shown in Table E2. Anemia, iron deficiency, and vitamin D insufficiency were not associated with infection or disease (case–control studies 1 and 2, Tables E3 and E4).

Table 3. Comparison of reported dietary intake between subjects with new infection or no infection (Case–Control Study 1)

Dietary intake	New Infection with Inadequate Intake *n* (%)	Uninfected with Inadequate Intake *n* (%)	Adjusted OR for New Infection* OR_{adj} (95% CI)
Total subjects	**88 (—)**	**67 (—)**	
Food group			
Grain	74 (84.1)	52 (77.6)	1.01 (0.3–3.4)
Fruit and vegetables	53 (60.2)	23 (34.4)	**2.1 (1.0–4.3)**
Dairy	69 (78.4)	44 (65.7)	1.7 (0.7–3.8)
Meat and equivalent	18 (20.5)	7 (10.4)	2.3 (0.9–5.8)
Nutrient			
Energy	33 (37.5)	17 (25.4)	2.2 (1.0–5.1)
Protein	13 (14.8)	2 (3.0)	4.9 (0.9–25.8)
Total lipids	10 (11.4)	3 (4.5)	3.8 (0.9–16.8)
Carbohydrates	12 (13.6)	5 (7.5)	**4.4 (1.2–16.3)**
Dietary fiber	71 (80.7)	55 (80.6)	1.4 (0.5–3.9)
Vitamin A	57 (64.8)	24 (35.8)	**2.8 (1.3–6.2)**
Vitamin D	28 (31.8)	17 (25.4)	1.5 (0.7–3.5)
Vitamin C	19 (21.6)	5 (7.5)	2.1 (0.7–7.0)
Thiamin	22 (25)	7 (10.4)	**3.3 (1.2–9.5)**
Riboflavin	14 (15.9)	3 (4.5)	3.9 (1.0–16.2)
Niacin	17 (19.3)	5 (7.5)	**3.8 (1.1–12.6)**
Folate	47 (53.4)	18 (26.9)	**3.0 (1.3–6.7)**
Vitamin B6	16 (18.2)	5 (7.5)	2.8 (0.8–9.3)
Vitamin B12	3 (3.4)	2 (3.0)	0.6 (1.0–5.2)
Calcium	71 (80.7)	45 (67.2)	1.3 (0.5–3.3)
Magnesium	48 (54.5)	19 (28.4)	**2.8 (1.3–6.3)**
Phosphorous	18 (20.5)	10 (14.9)	2.0 (0.8–5.4)
Iron	23 (26.1)	10 (14.9)	**2.6 (1.0–6.9)**
Zinc	31 (35.2)	14 (20.9)	2.3 (1.0–5.4)
Selenium	11 (12.5)	2 (3.0)	**5.9 (1.1–32.6)**
Sodium	43 (48.9)	29 (43.3)	1.5 (0.7–3.2)

Definition of abbreviations: CI = confidence interval; OR_{adj} = adjusted odds ratio.
Bolded odds ratios indicate $P < 0.05$.
*Among those with inadequate intake, adjusted for age, sex, living with a person with smear-positive tuberculosis, visiting a gathering house, accounting for clustering at the household level at the time of the survey.

Lifestyle and Drug and Alcohol Use

There were no significant differences between adults who completed and those who did not complete the lifestyle survey (Table E5). Among adults who completed the questionnaires, 83.8% were current smokers, 60.0% used alcohol in the last month, and 63.8% used cannabis within the last month.

Visiting a community gathering house (popular communal meeting places in this community) was more common among those who used cannabis (odds ratio [OR], 3.4; 95% confidence interval [CI], 1.2–9.6) or any illicit drugs (OR, 3.1; 95% CI, 1.1–8.7).

Combined Multivariable Analyses

Multivariable comparisons between different exposure, nutrient, and environmental variables (Table 5) found that new infection (in case–control study 1) was associated with an increase in age stratum (OR, 2.5; 95% CI, 1.3–4.9), living with a person with smear-positive tuberculosis (OR, 14.7; 95% CI, 1.6–137.3), visiting a gathering house (OR, 3.7; 95% CI, 1.7–8.3), increased room occupancy (OR, 2.0; 95% CI, 1.1–3.8), fruit and vegetable intake lower than recommended (OR, 2.3; 95% CI, 1.01–5.1), and low vitamin A intake (OR, 2.5; 95% CI, 1.1–5.9). Cigarette smoking was associated with new infection in the multivariable analysis among individuals who completed the lifestyle survey (OR, 9.4; 95% CI, 1.2–71.6). Prior infection was protective against disease (OR, 0.2; 95% CI, 0.1–0.7). There were no associations found between disease (in case–control study 2) and nutrition, housing, or lifestyle factors in the multivariable analysis (Table E6).

Discussion

Since 2003, a resurgence of tuberculosis has been reported among Inuit of Nunavik, Nunavut, and Greenland (30). Although clear evidence is lacking, this has been attributed to socioeconomic and environmental factors (31), given that poverty is substantially more common in these regions than in the rest of Canada (32). This study was motivated by this resurgence in light of an outbreak in an Inuit community in Nunavik, characterized by a very high number of newly infected

Table 4. Comparison of reported dietary intake between subjects with active disease versus no disease among all subjects with new and prior infection (Case–Control Study 2)

Nutrient	All Infection (New and Prior)		Adjusted Odds of Disease* OR (95% CI)
	Disease with Inadequate Intake (*Total n* = *43*) *n* (%)	No Disease with Inadequate Intake (*Total n* = *89*) *n* (%)	
Food group			
Grain	33 (76.7)	81 (91.0)	0.45 (0.2–1.4)
Fruit and vegetables	20 (46.5)	55 (61.8)	0.42 (0.2–1.0)
Dairy	28 (65.1)	68 (76.4)	0.43 (0.2–1.1)
Meat and equivalent	6 (14)	26 (29.2)	0.36 (0.1–1.0)
Nutrient			
Energy	13 (30.2)	29 (32.6)	0.66 (0.3–1.6)
Protein	3 (7)	15 (16.9)	0.29 (0.1–1.1)
Total lipids	4 (9.3)	7 (7.9)	0.77 (0.2–3.0)
Carbohydrates	5 (11.6)	11 (12.4)	0.70 (0.2–2.3)
Dietary fiber	32 (74.4)	69 (77.5)	0.54 (0.2–1.6)
Vitamin A	23 (53.5)	52 (58.4)	0.66 (0.3–1.6)
Vitamin D	13 (30.2)	28 (31.5)	0.85 (0.4–2.0)
Vitamin C	6 (14)	21 (23.6)	0.43 (0.1–1.3)
Thiamin	10 (23.3)	20 (22.5)	0.87 (0.3–2.2)
Riboflavin	5 (11.6)	14 (15.7)	0.53 (0.2–1.7)
Niacin	6 (14)	15 (16.9)	0.62 (0.2–1.8)
Folate	20 (46.5)	42 (47.2)	0.80 (0.4–1.8)
Vitamin B6	4 (9.3)	18 (20.2)	0.29 (0.1–1.0)
Vitamin B12	0 (0)	4 (4.5)	na
Calcium	29 (67.4)	67 (75.3)	0.55 (0.2–1.4)
Magnesium	22 (51.2)	45 (50.6)	0.91 (0.4–2.1)
Phosphorous	6 (14)	17 (19.1)	0.55 (0.2–1.6)
Iron	11 (25)	21 (23.6)	0.99 (0.4–2.4)
Zinc	14 (32.6)	30 (33.7)	0.75 (0.3–1.8)
Selenium	3 (7)	13 (14.6)	0.38 (0.1–1.5)
Sodium	19 (44.2)	36 (40.4)	0.95 (0.4–2.1)

Definition of abbreviations: CI = confidence interval; na = not applicable, as zero events in one group; OR_{adj} = adjusted odds ratio.
*Among subjects with inadequate intake, adjusted for age, sex, personal income, current smoking status, and prior infection, accounting for clustering at the household level at the time of the survey.

individuals, of whom 28% developed disease within months of exposure. We found that an inadequate intake of fruit and vegetables, and several specific nutrients, was associated with an increased risk of new infection. However, despite carefully characterizing many potential dietary, lifestyle, and social determinants, we did not find strong evidence that any single factor was responsible for this high rate of disease.

Untangling the nexus between concurrent socioeconomic factors and tuberculosis is challenging in settings where tuberculosis is prevalent—given the close relationship between poverty, tuberculosis, and their determinants (2, 31). Poor nutrition can be both cause and effect of the disease (33). Ecological studies of populations at risk for tuberculosis have reported associations between socioeconomic factors and disease (2, 34); however, their findings are limited by problems of unmeasured confounding. Hence, the careful characterization of a large number of potential determinants of latent tuberculosis infection and disease was an additional strength of this study. These included demographic housing, social, environmental, and lifestyle factors, as well as the HIV status of people with disease. Although this inevitably means that the results of our comparative analyses should be considered hypothesis generating only, nevertheless, the estimates of effect of each potential social determinant could be adjusted for the potentially confounding effects of other possible determinants. Furthermore, as malnutrition is widespread among patients with tuberculosis, further studies into the relationship between nutrition, socioeconomic factors, and tuberculosis in other settings are also warranted.

The study had a number of important limitations. One of the most important was the 1-year delay between the occurrence of the outbreak and this study to investigate it. However, it was simply impossible, for ethical and practical reasons, to conduct this in-depth study during the outbreak. During the start of the outbreak, the clinical and public health workers were severely overburdened, and the entire village population was involved with screening, diagnostic, and treatment efforts. The 1-year interval between occurrence of infection and disease and this study meant that participant responses may have changed, particularly regarding lifestyle habits or diet, potentially resulting in misclassification bias.

Another limitation was that 94% of those with new infection were treated with isoniazid during the outbreak. This may have attenuated any effect of nutrition

Table 5. Combined univariable and multivariable models for new infection comparing uninfected and newly infected subjects, for all subjects and those completing the lifestyle survey (Case–Control Study 1)

Parameter	All Subjects (*n* = 155)* Univariable Analyses OR (95% CI)	Multivariable Analysis OR (95% CI)	Subjects Completing Lifestyle Survey (*n* = 65)[†] Multivariable Analysis OR (95% CI)
Variables adjusted in model			
Age stratum[‡]	**2.6 (1.5–4.4)**	**2.5 (1.3–4.9)**	0.5 (0.1–2.3)
Male sex[‡]	1.0 (0.5–1.8)	1.1 (0.5–2.4)	1.5 (0.4–5.1)
Lived with person with smear-positive TB[‡]	**19.4 (2.5–149)**	**14.7 (1.6–137)**	0.9 (0.1–12.9)
Visited gathering house[‡]	**3.7 (1.8–7.4)**	**3.7 (1.7–8.3)**	3.2 (0.8–13.3)
High room occupancy among households with a smear positive resident[§]	2.8 (0.6–12)	**2.0 (1.1–3.8)**	2.5 (0.1–80.0)
High room occupancy among households with no smear positive resident[§]	1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.7 (0.5–1.1)
Fruit and vegetable intake below recommended[‡‖]	**2.9 (1.5–5.6)**	**2.3 (1.01–5.1)**	2.8 (0.7–11.0)
Other dietary variables			
Energy intake below recommended[‖]	1.8 (0.9–3.6)	1.5 (0.6–3.8)	1.0 (0.2–3.9)
Magnesium intake below recommended[‖]	**3.0 (1.5–6.0)**	1.9 (0.7–5)	1.1 (0.2–4.9)
Vitamin A intake below recommended[‖]	**3.3 (1.7–6.4)**	**2.5 (1.1–5.9)**	2.9 (0.7–13.2)
Other lifestyle variables			
Food insecure	1.5 (0.7–3.2)	1.6 (0.7–3.4)	1.6 (0.7–3.4)
Personal income <$20,000/year	1.5 (0.8–2.9)	1.4 (0.7–3.2)	2.6 (0.6–11.2)
Current cigarette smoking	**2.9 (1.5–5.5)**	**0.8 (0.4–1.8)**	**9.4 (1.2–72.0)**
Recent alcohol use	na	na	0.7 (0.2–2.6)
Recent cannabis use	na	na	1.1 (0.3–4.5)

Definition of abbreviations: CI = confidence interval; na = not applicable, as data on substance use only collected by those who completed the Lifestyle Survey; OR = odds ratio.
Bolded results indicate that the 95% CI does not include 1.00 (i.e., $P < 0.05$).
*Includes all newly infected (*n* = 88) and uninfected (*n* = 67) individuals, shown in Figure 2A.
[†]Includes newly infected (*n* = 48) and uninfected (*n* = 17) individuals, shown in the Figure 2B.
[‡]Variables for which all multivariable analyses were adjusted included age stratum, sex, living with a person with smear-positive tuberculosis, visiting a gathering house, room occupancy, and low vegetable intake. An interaction term between room occupancy and living with a person with smear-positive tuberculosis was included. Additional dietary variables were not included in the multivariable model on account of collinearity, evaluated on a covariate matrix.
[§]Each unit increase represents an increase in occupancy of one unit, which correlates to an increase in 0.2 adults per room (i.e., one additional adult per five-bedroom house).
[‖]Recommended daily intake, defined according to North American and Canadian references (15, 17, 19–21).

upon progression to disease, given that some infected subjects in case–control study 2 might have developed disease if they had not been treated. In addition, the precision of our estimates was limited by the small numbers included in some of the regression models. Hence, further studies replicating these findings in larger cohorts are required. In addition, blood collection was performed regardless of fasting status. This may have introduced additional variability in the levels of some vitamins and potentially resulted in nondifferential misclassification bias (35).

This study has a number of implications. The high rate of disease after new infection indicates that this population is very susceptible to developing disease soon after infection. This was not explained by HIV infection or drug resistance in this outbreak. We cannot exclude genetic factors as contributing to the substantial susceptibility of this population to progress from infection to disease. Certainly, rare genetic variants can cause extreme susceptibility in a small proportion of individuals; however, the relative risk of common variants at a population level has tended to be modest (36). Nonetheless, this question warrants further study. Interestingly, contacts with prior infection overall had a 70% lower risk of disease than those who were not previously infected. This is similar to estimates of the protective effect of prior infection from the preantibiotic era (37), suggesting some degree of immune protection.

Second, dietary inadequacies were common and likely reflect the progressive shift from traditional to store-bought food, which now represents over 89% of the total daily food intake. This transition from a traditional diet to a Western diet has been observed in other Inuit communities (38, 39). Anemia and deficiencies of iron and vitamin D were substantially more common than in the Canadian general population (25, 40). The latter may reflect both inadequate dietary intake and lower rates of sun exposure than with traditional lifestyles (41), as vitamin D levels reflect the contribution of both sources. Given these findings, and high rates of food insecurity in this community, broader interventions providing improved access to nutritious foods are warranted to improve the overall health population (42).

In summary, this study has explored the complex effect of social, lifestyle, dietary, and environmental factors upon susceptibility to infection and disease. These findings generate additional hypotheses. We suggest that intervention studies, aiming to improve food security and increase access to healthy foods, should be considered. In conjunction with established tuberculosis control strategies, such approaches may improve the resilience of disadvantaged communities, and mitigate the impacts of future tuberculosis outbreaks. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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