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Association of low FVC spirometric pattern with WTC occupational exposures

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ABSTRACT

Background: A reduced forced vital capacity without obstruction (low FVC) is the predominant spirometric abnormality reported in workers and volunteers exposed to dust, gases, and fumes at the World Trade Center (WTC) disaster site in 2001–2002. While low FVC has been associated with obesity and metabolic syndrome, its association with WTC occupational exposures has not been demonstrated. We estimated the prevalence of this abnormality and examined its association with WTC exposure level.
Methods: Longitudinal study of the relation between arrival at the WTC site within 48 h and FVC below the lower limit of normal (FVC < LLN, with normal FEV_1/FVC ratio) at any time in 10,284 workers with at least two spirometries between 2002 and 2018. Logistic regression and linear mixed models were used for the multivariable analyses.
Results: The prevalence of low FVC increased from 17.0% (95% CI 15.4%, 18.5%) in June 2003, to 26.4% (95% CI 24.8%, 28.1%) in June 2018, and exceeded at both times that of obstruction. The rate of FVC decline was −43.7 ml/year during the study period. In a multivariable analysis adjusting for obesity, metabolic syndrome indicators, and other factors, early arrival at the WTC disaster site was significantly associated with low FVC, but only among men (OR_{adj} = 1.29, 95% CI 1.17, 1.43). Longitudinal FVC rate of decline did not differ by WTC site arrival time.
Conclusions: Among WTC workers, the prevalence of low FVC increased over a 16-year period. Early arrival to the WTC disaster site was significantly associated with low FVC in males.

1. Introduction

Occupational exposures at the World Trade Center (WTC) disaster site in 2001–2002 have been associated with a variety of adverse health effects [1], including a heterogeneous, often not easily classifiable group of chronic lower airway diseases [1,2]. In all cohorts with lung function data, the most consistent and frequently reported spirometric ventilatory impairment pattern has been that of reduced forced vital capacity (low FVC), with obstruction being considerably less frequent [1,3–7].

In 2009, a report of longitudinal expiratory flow trajectories in the largest and most diverse occupational WTC cohort, was based on only two spirometries per subject [8]. In that study, the decline rate in lung function was normal or what was expected with aging: the mean decline in prebronchodilator FVC and first second forced expiratory flow (FEV_1) were −13 and −2 ml/year, respectively. Moreover, the only identified predictors of more rapid decline in FEV_1 and FVC were lack of bronchodilator responsiveness at the baseline examination, and weight gain between examinations, with these two factors accounting, however, for no more than 10% of the variance in lung function decline. A more recent report of a sub-cohort of WTC responders [7], identified a larger

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average FEV_1 decline (−35.7 ml/year), more widely divergent longitudinal FEV_1 trajectories, and quantitative chest CT measured wall area percent, age at baseline, presence of bronchodilator response, and lack of significant pre-WTC occupational exposures as significant predictors. Importantly, neither study identified WTC occupational exposure indicators as significant predictors.

On the basis of previous findings, we conducted an updated analysis of decline in FVC in the WTC cohort, 18 years after the disaster, using also an updated definition of low FVC that requires absence of obstruction (i.e., FEV_1/FVC above lower limit of normal) [9]. Low FVC thus defined is emerging as a phenotype of chronic airway disease [9, 10]. Low FVC can, however, also result from a variety of factors, including obesity [11] (more prevalent in the WTC occupational cohorts [6,8,12,13] than in the general U.S. population [14]), short exhalatory time, and true lung restriction (i.e., reduced total lung capacity) [15]. We hypothesized that two previously proposed [1] WTC exposure level indicators, namely early arrival (within 48 h) to the disaster site and WTC exposure duration, would be associated with a reduced FVC, after adjusting for other risk factors in this and other WTC occupational cohorts [7,16,17], as well as in the general population [18].

2. Methods

2.1. Subjects and clinical data acquisition

All subjects participated in the screening, surveillance, and clinical programs of the WTC Clinical Center of Excellence at Mount Sinai Medical Center, in New York City [4,5]. The New York University School of Medicine IRB (i16-01412), and the Mount Sinai Program for the Protection of Human Subjects (HS 17–01098) approved the study. Details on subject recruitment, eligibility criteria, and screening and surveillance protocols have been previously reported [4]. In brief, participants were all workers and volunteers who performed rescue, recovery, and service restoration duties at the WTC disaster site from September 11, 2001 to June 2002. This open cohort includes all occupational groups that worked at the disaster site [19]. Beginning in July 2002, all subjects underwent a baseline screening evaluation, which included questionnaires on respiratory symptoms, pre-WTC- and WTC-related occupational exposures, physical examination, laboratory testing, spirometry, and chest radiograph (repeated on alternate visits). Subsequent ("monitoring") health surveillance visits included a similar evaluation at 12- to 18-month intervals, and clinical services were offered (often contiguously to the screening) for individualized diagnostic and treatment services [1,20]. Inclusion into this study required that the WTC workers had at least two screening and surveillance spirometries of adequate quality.

2.2. Spirometry

Spirometry was performed using the EasyOne® portable flow device (ndd, Zurich, Switzerland). Bronchodilator response (BDR) was assessed at least once (and most often at the baseline visit) by repeating spirometry 15 min after administration of 180 mcg of albuterol via metered dose inhaler and a disposable spacer. Predicted values for spirometric measurements were calculated for all subjects' acceptable tests, based on reference equations from the third National Health and Nutrition Examination Survey (NHANES III) [21], and all testing, quality assurance, ventilatory impairment pattern definitions, bronchodilator response presence, and interpretative approaches followed American Thoracic Society recommendations [22–24]. Spirometries in this study were selected if performance had been acceptable, and they had a good quality, based on computer quality grade (a measure of reproducibility) [24] A or B, or C if at least 5 trials had been obtained, and a forced exhalatory time of at least 6 s [9].

2.3. Statistical analysis

Presentation of descriptive data included means and standard deviations (SD), medians and interquartile ranges (IQR), or counts and proportions, as appropriate. We employed simple logistic regression for unadjusted analyses, and standardized differences (StD) [25] to compare subjects included and excluded from the study. For the latter, we considered a standardized difference$\geq$0.2 as indicating a significant effect size of a covariate. Cross-sectional prevalence of low FVC was determined by the occurrence of that pattern among all subjects tested within the year preceding June 30, 2003, and June 30, 2018, respectively.

Our outcome of interest was having low FVC, defined as both a measured pre-bronchodilator FVC below each individual's predicted lower limit of predicted normal value (LLN), and a normal ratio of first-second forced expiratory volume to FVC (FVC $<$ LLN and FEV_1/FVC $>$ LLN, low FVC). Our dichotomous predictor of interest was self-reported arrival at the WTC disaster site within 48 h at the WTC site. We employed multivariable logistic regression, using generalized estimating equations with an exchangeable correlation structure to account for repeated measures. For descriptive purposes, we estimated the prevalence of obstruction, defined as pre-bronchodilator evidence of FEV_1/FVC $<$ LLN.

The following covariates were included in the multivariable analyses: (1) cumulative WTC exposure duration, assessed at baseline, and categorized with more than 60 days as the cutpoint; (2) social and demographic variables, all assessed at baseline: age on September 11, 2001, gender, height, ethnicity/race (Latino of any race, and non-Latino White, Black, and other race), and occupation before 9/11/2001 (categorized into protective services, construction, building cleaning and maintenance and electrical, telecommunications, and other installation and repair group [BCM&IRG], and all other); (3) body mass index (BMI) at each evaluation, categorized into normal ($>$18 and $<$25 kg/m^2), overweight ($\geq$25 and $<$30 kg/m^2), and obese ($\geq$30 kg/m^2); (4) entry into the cohort, categorized into calendar years 2002–2005, 2006–2008, and 2009 and later; (5) evidence of bronchodilator response (dichotomous) at any visit; (6) smoking status at each visit, categorized into never, former and current smokers. A subject was considered a never smoker if (s)he had smoked less than 20 packs of cigarettes (or 12 oz. of tobacco) in a lifetime, or less than 1 cigarette/day (or 1 cigar/week) for one year. A minimum of 12 months without tobacco use was required to deem a subject a former smoker [26]; (7) highest recorded heart rate (cutpoint 90 beats per minute), diastolic blood pressure (cutpoint 90 mm Hg); (8) highest recorded serum glucose level (whether fasting or not, cutpoint 200 mg/dl), triglyceride level (whether fasting or not, cutpoint 300 mg/dl), eosinophil (cutpoint 351/mcl), and neutrophil (cutpoint 6,000/mcl) counts, and lowest recorded high-density lipoprotein (HDL, cutpoints 40 and 50 mg/dl for men and women, respectively). We used HDL, glucose, triglycerides, and diastolic blood pressure as surrogate indicators of probable metabolic syndrome (Metsyn), categorized as 0–1 and 2–4 indicators.

Collinearity among variables was excluded by the variance inflation factor. The dependent variable was the dichotomous outcome of whether a subject's FVC was below the lower limit of predicted normal, without obstruction (low FVC), at any time, and the main predictor, arrival within 48 h at the WTC disaster site. Interaction terms were examined, and stratified results were presented if found. We used multiple imputation with fully conditional specification to address missing responses among the independent variables, and performed sensitivity analysis without multiple imputation as a comparison. The results with the complete and imputed data sets were essentially identical, and we therefore present only the latter.

We also used linear mixed model with a random intercept to estimate the longitudinal rate of FVC decline for the cohort. In this multivariable model, the covariates were the same as in our main model, and all were estimated as fixed effects, with age on 9/11/2001 and height centered at the mean, and in 5-year, and 5-cm units, respectively.

A two-sided *p* value below 0.05 defined statistical significance. The SAS program, version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

3. Results

We had 33,093 spirometries on 10,284 subjects (mean 3.2, SD 1.4), followed for a mean of 7.2 (SD 4.1) years, until 30-June-2018. The cohort demonstrated the predominance of male sex (85.4%) and overweight and obesity (85.6%) typical of the WTC occupational cohorts. Fig. 1 shows the study flow chart. Compared to subjects excluded from this analysis, those included were slightly older, and more likely to be early entrants into the cohort, to meet at least 2 of the metabolic syndrome indicators, and to have higher neutrophil and eosinophil counts (Table OS1).

Table 1 shows the main characteristics of study participants. The mean age was 39.7 (SD 8.7) years on September 11, 2001, with the typical male predominance (85.4%), and overweight/obesity prevalence (85.6%) of the WTC occupational cohorts. The overall cross-sectional prevalence of low FVC in June 2003 was 17.0% (95% CI 15.4%, 18.5%), and was higher among those who arrived at the WTC within 48 h (18.5%, 95% CI 16.5%, 20.6%) vs. those who did not (14.5%, 95% CI 12.2%, 16.9%). That overall prevalence increased by June 2018 to 26.4% (95% CI 24.8%, 28.1%), being even more clearly higher among those who arrived at the WTC within 48 h (29.2%, 95% CI 27.0%, 31.4%) vs. those who did not (22.0%, 95% CI 19.4%, 24.6%). In contrast, the prevalence of obstruction was 10.5% and 5.9% in June 2003 and June 2018, respectively, and was not significantly associated with WTC arrival within 48 h in either unadjusted or adjusted analyses (data not presented). The rate of longitudinal decline in FVC for the cohort was −43.7 (95% CI -42.9, −44.5) ml/year, and did not differ by WTC arrival time.

Unadjusted comparisons (Table OS2) showed that low FVC was associated with our main WTC occupational exposure indicator, arrival within 48 h at the disaster site, but sex modified the effect, so that the effect was restricted to men (OR 1.43, 95% CI 1.30, 1.58). All the covariates were also associated, except for cumulative WTC exposure duration, smoking status at each visit, and eosinophil count. The association of early arrival at the WTC site for men was confirmed after adjustment for covariates (OR_{adj} 1.29, 95% CI 1.17, 1.43, see Table OS2). The multivariable analysis confirmed all the unadjusted associations, except for cohort entry period. There were no significant interactions between WTC early arrival and occupational exposure duration, age, probable MetSyn, or smoking status at each visit on its effect on low FVC.

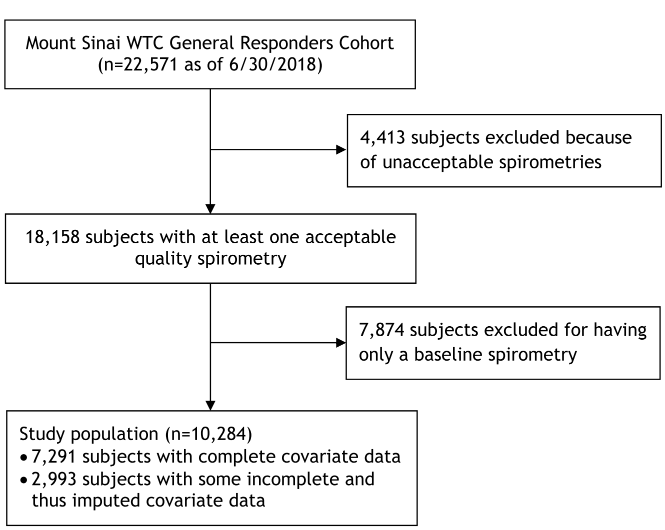

Fig. 1. Study flowchart.

4. Discussion

In this 16-year longitudinal study, we estimated the prevalence of low FVC, the most frequently reported ventilatory impairment pattern seen in this diverse occupational WTC cohort, and its increase over time. We demonstrate for the first time an association between more intense occupational WTC dust, as suggested by early arrival (within 48 h) at the WTC disaster site [1] and low FVC. This association is independent from risk factors for adverse respiratory outcomes in this [7] and other cohorts [27], such as overweight and obesity, current smoking, bronchodilator response [7], having a pre-WTC occupational category other than construction, high peripheral blood neutrophil counts, meeting at least 2 indicators suggestive of the metabolic syndrome [18], and having a higher heart rate [28]. We confirmed a previous observation [1] of the relative lack of significance of the association of adverse respiratory health effects with WTC exposure duration in this cohort.

This is the first study to focus on the predominant spirometric abnormality of the WTC responders and, accordingly, to restrict the analyses to spirometries with a minimum of 6 s of forced exhalatory time, besides acceptable reproducibility criteria (quality grades). The low FVC prevalence in this WTC cohort substantially exceeds the 8.2% and 7.1% estimates among participants aged 40–59 in NHANES III in 1988–1994, and 2007–2010, respectively [29], and that of obstruction. Low FVC (when not explained by true restriction) is emerging as a phenotype of chronic airway disease [30–32] and has been associated with significant morbidity [33–41] and mortality [38,42]. Quantitative chest computed tomography data from other studies [39], and our own [43], demonstrated evidence suggestive of proximal airway inflammation in individuals with low FVC. Those results do not exclude distal airway disease [44] and, indeed, other lines of evidence have suggested that low FVC impairment by spirometry [45] or in response to bronchial challenge testing [46] may result from loss of lung units in parallel distally to obstructed bronchioles. Additionally, unadjusted impulse oscillometric data in a WTC-exposed community resident and worker case series reported evidence of increased distal airway resistance [47]. Although low FVC is often a stable disease state, it has also been shown to be sometimes a transitional state to and from both normal lung function and COPD, respectively [48]. Low FVC can also result from true restriction, but this is less likely in cohorts with high prevalence of overweight and obesity [55]. While no evidence of an increased incidence of interstitial lung disease has been documented in the WTC occupational cohorts, in subsets with chest CT scans [6], there is evidence of mostly mild interstitial lung abnormalities in a small proportion of these workers, which warrant continued longitudinal observation, but are unlikely to explain the observed prevalence of low FVC. The observation of the effect restricted to men, the majority (85.4%) of our cohort, may be explained by the relative small number of women, a differential sex-related effect, or residual confounding by another variable.

Low FVC (unrelated to true restriction) is not generally recognized as associated with occupational exposures [9], although previous occupational studies (e.g., among grain elevator workers [49]) had already demonstrated it. Our study provides additional support for that association, but also finds a relatively normal age-related mean rate of longitudinal expiratory flow decline, which is consistent with a single "hit and shift" trajectory, as reported in WTC occupational cohorts [7,8,50]. That seemingly normal mean age-related longitudinal expiratory flow decline is not surprising in a population who was not heavily smoking at baseline [1,43] and whose smoking prevalence seems to have declined over time [43], but it also hides significantly divergent trajectories with accelerated decline and unexpected gain in subsets of the cohort [7].

Our study had the added advantage of examining one of the largest, and most sociodemographically diverse occupational WTC cohorts [19]. This cohort has the richest spirometry data set and is unique in that more

Table 1
Characteristics of 10,284 WTC responders, with stratification by the main predictor of interest, arrival at the WTC disaster site within 48 h of the terrorist attack on September 11, 2001.

				Arrival at the WTC disaster site					
Characteristic	value	Entire group		≤48 h		>48 h		Missing	
		n or mean	% or SD	n or mean	% or SD	n or mean	% or SD	n or mean	% or SD
Arrival at WTC disaster site	≤48 h	6,338	61.6	6,338	61.6	–	–		
	>48 h	3,868	37.6	–	–	3,868	37.6	–	–
	Missing	78	0.8	–	–	–	–	78	0.8
Age on 9/11	Years	39.7	8.7	39.4	8.2	40.4	9.3	39.6	10.1
Sex	Female	1,505	14.6	721	11.38	771	19.93	13	16.67
	Male	8,779	85.4	5,617	88.62	3097	80.07	65	83.33
Ethnicity/race	Non-Latino/Black	1.289	12.5	854	13.47	425	10.99	10	12.82
	Non-Latino/White	5,612	54.6	3,724	58.76	1850	47.83	38	48.72
	Latino/any race	3,086	30.0	1,552	24.49	1507	38.96	27	34.62
	Non-Latino/Other	230	2.2	163	2.57	64	1.65	3	3.85
	Missing	67	0.7	45	0.71	22	0.57	–	–
Height	cm	173.7	9.4	175.2	8.6	171.4	10.1	172.6	10.3
BMI category	Normal	1,484	14.4	818	12.91	654	16.91	12	15.38
	Overweight	4,625	45.0	2,765	43.63	1826	47.21	34	0.33
	Obese	4,175	40.6	2,755	43.47	1388	35.88	32	41.03
Cohort entry period	2002–2005	6,218	60.5	3,708	58.50	2473	63.93	37	47.44
	2006–2008	2,708	26.3	1,704	26.89	978	25.28	26	33.33
	2009+	1,358	13.2	926	14.61	417	10.78	15	19.23
Smoking status	Never smoker	6,075	59.1	3,857	60.86	2172	56.15	46	58.97
	Former smoker	2,580	25.1	1,560	24.61	1001	25.88	19	24.36
	Current smoker	1,434	13.9	816	7.93	606	5.89	12	0.12
	Missing	195	1.9	105	1.66	89	2.30	1	1.28
Pre-WTC occupation group	Construction	2,716	26.4	1,186	18.71	1524	39.40	6	7.69
	BCM&IRG[a]	1,061	10.3	517	8.16	539	13.93	5	6.41
	Other	2,193	21.3	1,181	18.63	950	24.56	62	79.49
	Protective	4,314	42.0	3,454	54.50	855	22.10	5	6.41
WTC exposure duration	<60 days	4,897	47.6	3,225	50.88	1665	43.05	7	8.97
	>60 days	5,321	51.7	3,113	49.12	2202	56.93	6	7.69
	Missing	66	0.6	–	–	1	0.03	65	83.33
Bronchodilator response	Absent	8,121	79.0	4,991	78.75	3071	79.40	59	75.64
	Present	1,537	15.0	939	14.82	583	15.07	15	19.23
	Missing	626	6.1	408	3.97	214	2.08	4	0.04
Probable Metsyn[b]	0-1 criteria	8,377	81.5	5,188	81.86	3130	80.92	59	75.64
	2-4 criteria	1,888	18.4	1,143	18.03	727	18.80	18	23.08
	Missing	19	0.2	7	0.11	11	0.28	1	1.28
Heart rate	≤90 bpm	10,002	97.3	6,166	97.29	3763	97.29	73	93.59
	>90 bpm	254	2.5	156	2.46	95	2.46	3	3.85
	Missing	28	0.3	16	0.25	10	0.26	2	2.56
Eosinophil count	≤300/mcl	8,221	79.9	5,151	81.27	3009	77.79	61	78.21
	>300/mcl	2,042	19.9	1,179	18.60	847	21.90	16	20.51
	Missing	21	0.2	8	0.13	12	0.31	1	1.28
Neutrophil count	≤6000/mcl	7,573	73.6	4,649	73.35	2873	74.28	51	65.38
	>6000/mcl	2,690	26.2	1,681	26.52	983	25.41	26	33.33
	Missing	21	0.2	8	0.13	12	0.31	1	1.28

[a] BCM&IRG: buildings and grounds cleaning and maintenance, and electrical, telecommunications and other installation and repair groups.
[b] Probable Metsyn: probable metabolic syndrome.

than 80% of the subjects had bronchodilator responsiveness testing since 2002, usually at their baseline examination, and irrespective of clinical status. The spirometry quality requirements for our study sought to exclude suboptimal performance, reproducibility, expiratory effort, and (uniquely in the occupational WTC studies to date) short (<6 s) forced exhalatory time. We also adjusted longitudinally for substantial and highly prevalent potential confounders (notably, obesity and smoking), and for many metabolic and cardiovascular risk factors that have been reported in association with low FVC [9,33–36]. Selection bias due to differential loss to follow-up is a possible but unlikely explanation for our findings, given the observed differences between subjects who were and were not included in this analysis.

Study limitations include the lack of pre-WTC lung function data in the vast majority of subjects, as well as a suitable unexposed comparison population. We also lacked total lung capacity measurements to exclude true restriction in all subjects with low FVC, as plethysmography is not part of the surveillance program. CT imaging is similarly not part of the surveillance program, but available data suggests only mild interstitial lung abnormalities in about 10% of a subset of that subcohort [6]. We lacked detailed pre-WTC occupational exposure data. In a previous study with a subset of this cohort, we demonstrated that those pre-WTC occupational exposures (e.g., to asbestos) are indeed potentially relevant, and can be associated with CT scan abnormalities such as pleural thickening [6], but not lung nodules [51]. Similar to essentially all WTC-related studies, we lack direct toxicant exposure data, as the exposure hazards were grossly underestimated [52], and detailed exposure studies were extremely limited in size [53]. The latter and clinical data [1], in turn, support the empirically derived occupational exposure indicators based on early arrival at the disaster site. A clinical study in a small subset of this cohort [1] had already reported unadjusted association of WTC-related lower airway disease with arrival at the WTC disaster site within 48 h (before the first rain, that in all likelihood helped settle dust), and the lack of association of WTC exposure duration with this adverse respiratory outcome. Finally, although there are still some differences in the definition of low FVC impairment across studies [9], the best designed amongst them generally share requirements for both reduction in FVC and exclusion of obstruction in their definition (whether using a fixed percentage or statistical lower limit of normal to define them), while they may or may not require a concomitant FEV_1 reduction [9,32]. Our results did not vary with the inclusion of the latter criterion (data not presented), and we focused our efforts on the more important [9], and unprecedented requirement (among large occupational WTC studies) [54] of >6 s forced exhalatory times for all spirometries.

In conclusion, we demonstrated that occupational WTC exposure intensity, as indicated by arrival at the disaster site within the first 48 h, was associated with low FVC, by far the most prevalent spirometric abnormality in this diverse cohort of WTC workers and volunteers, and the high prevalence of that abnormality is not only persisting but increasing after 16 years of follow up, independently from obesity, smoking, and other potential risk factors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported by cooperative agreements No. U01 OH011300 (AN, PI), U01 OH010401 and U01 OH011697 (RED, PI), and contract 200-2017-93325 (WTC General Responders Cohort Data Center, RGL, PI) from the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDCP/NIOSH). The authors had no other relevant financial conflict of interest. The contents of this article are the sole responsibility of the authors and do not necessarily represent the official views of the CDCP/NIOSH.

CRediT authorship contribution statement

Rafael E. de la Hoz: Formal analysis, Writing - original draft, Writing - review & editing. **Moshe Shapiro:** Formal analysis, Writing - original draft, Writing - review & editing. **Anna Nolan:** Formal analysis, Writing - original draft, Writing - review & editing. **Juan C. Celedón:** Writing - original draft, Writing - review & editing. **Jaime Szeinuk:** Writing - original draft, Writing - review & editing. **Roberto G. Lucchini:** Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106058.

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