COVID-19-like symptoms and their relation to the SARS-CoV-2 epidemic in children and adults of an Italian birth cohort

Maja Popovic 1 , Chiara Moccia 2 , Elena Isaevska 2 , Giovenale Moirano 2 , Costanza Pizzi 2 , Daniela Zugna 2 , Franca Rusconi 3 , Franco Merletti 2 , Milena Maule 2 , Lorenzo Richiardi 2

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Epidemiol Prev 2021;45:In press.
doi: 10.19191/EP21.6.093.

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Sintomi tipici del COVID-19 nei bambini e negli adulti della coorte di nascita italiana NINFEA e la loro relazione con l'epidemia di SARS-CoV-2

Maja Popovic[1], Chiara Moccia[1], Elena Isaevska[1], Giovenale Moirano[1], Costanza Pizzi[1], Daniela Zugna[1], Franca Rusconi[2], Franco Merletti[1], Milena Maule[1], Lorenzo Richiardi[1]

Affiliations

[1] Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, and Reference Centre for Epidemiology and Cancer Prevention in Piemonte (CPO Piemonte), Turin, Italy
[2] Unit of Epidemiology, Meyer Children's University Hospital, Florence, Italy

Corresponding author

Maja Popovic
Cancer Epidemiology Unit
Department of Medical Sciences
University of Turin
Via Santena 7
10126 Turin, Italy
tel +39 011 6334628
e-mail: maja.popovic@unito.it

Abstract

Objectives We aimed at estimating the population prevalence of COVID-19-like symptoms in children and adults during the first SARS-CoV-2 epidemic wave hitting Italy in the spring 2020, assess their geographical correlation with the cumulative number of COVID-19 cases by province, analyse their clustering within families, and estimate their sensitivity, positive predictive value (PPV) and negative predictive value (NPV) for COVID-19 diagnosis in individuals tested for SARS-CoV-2.

Design Cross-sectional study nested within a birth cohort.

Setting and participants Mothers participating in an Italian NINFEA birth cohort were invited to complete an online questionnaire on COVID-19-like symptoms in their household.

Main outcome measures Population prevalence of COVID-19-like symptoms in children and adults, geographical correlation of COVID-19-like symptoms with the cumulative number of COVID-19 cases by province, clustering of COVID-19-like symptoms within families, and sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of COVID-19-like symptoms for COVID-19 diagnosis in individuals tested for SARS-CoV-2.

Results Information was collected on 3184 households, 6133 adults, and 5751 children. In the period March-April 2020, 55.4% of the NINFEA families had at least one member with at least one COVID-19-like symptom. There was a strong geographical correlation between the population

cumulative incidence of COVID-19 and the prevalence of muscle pain, fatigue, low-grade fever, and breathing difficulties in adults (Spearman's rho ≥0.70). Having at least one family member with a COVID-19 diagnosis, compared with none tested for SARS-CoV-2, was associated with an increased prevalence ratio (PR) of almost all COVID-19-like symptoms in adults, and only of low-grade fever (37-37.5°C; PR 4.54; 95% confidence intervals: 2.20 to 9.40) and anosmia/dysgeusia in children. Among adults with COVID-19 diagnosis, fatigue, muscle pain, and fever had a sensitivity ≥70%. In individuals tested for SARS-CoV-2, with a 16.6% prevalence of COVID-19, breathing difficulties and nausea/vomiting had the highest PPVs, with point estimates close to 60%, and with NPVs close to 90%.

Conclusions The geographical prevalence of COVID-19-like symptoms in adults may inform on local disease clusters, while certain symptoms in family members of confirmed COVID-19 cases could help identify the intra-familial spread of the virus and its further propagation in the community. Low-grade fever is frequent in children with at least one household member with COVID-19 and possibly indicates child infection.

Key words: COVID-19, SARS-CoV-2, symptoms, Italy, NINFEA

Riassunto

Obiettivi Gli obiettivi di questo studio consistono nell'indagare la prevalenza dei sintomi tipici del COVID-19 nella popolazione pediatrica e adulta durante la prima ondata epidemica di SARS-CoV-2 che ha colpito l'Italia nella primavera 2020, valutare la loro correlazione geografica con il numero cumulativo di casi di COVID-19 per provincia, analizzare il clustering dei sintomi all'interno delle famiglie, e, infine, stimare la loro sensibilità, il valore predittivo positivo (PPV) e il valore predittivo negativo (NPV) per la diagnosi di COVID-19 tra gli individui testati per SARS-CoV-2.

Disegno Studio trasversale annidato all'interno di una coorte di nascita.

Setting e partecipanti Nell'aprile 2020, le madri partecipanti alla coorte NINFEA sono state invitate a completare un questionario anonimo online sui sintomi tipici del COVID-19 nei membri della propria famiglia.

Principali misure di outcome La prevalenza dei sintomi tipici del COVID-19 nella popolazione pediatrica e adulta, la loro correlazione geografica con il numero cumulativo di casi di COVID-19 per provincia, la sensibilità, il PPV e il NPV per la diagnosi di COVID-19 tra gli individui testati per SARS-CoV-2.

Risultati Lo studio ha coinvolto 6133 adulti e 5751 bambini per un totale di 3184 famiglie. Nel periodo marzo-aprile 2020, il 55,4% delle famiglie NINFEA aveva almeno un membro con almeno un sintomo tipico del COVID-19. È emersa una forte correlazione geografica tra l'incidenza cumulativa di COVID-19 nella popolazione e la prevalenza di dolori muscolari, stanchezza, febbre bassa e difficoltà respiratorie negli adulti (rho di Spearman ≥0.70). Avere almeno un membro della famiglia con diagnosi di COVID-19, rispetto all'assenza di testati nel nucleo familiare, è risultata essere associata negli adulti con un aumento del rapporto di prevalenza di quasi tutti i sintomi tipici del COVID-19, mentre nei bambini solo con febbre bassa (37-37.5 °C; rapporto di prevalenza 4.54; intervalli di confidenza al 95%: da 2.20 a 9.40) e anosmia/disgeusia. Tra gli adulti con COVID-19, stanchezza, dolore muscolare e febbre avevano una sensibilità ≥70%. Negli individui testati per

SARS-CoV-2, con una prevalenza di COVID-19 del 16.6%, difficoltà respiratorie e nausea/vomito hanno avuto i PPV più alti, con stime puntuali vicine al 60% e con NPV vicini al 90%.

Conclusioni

La prevalenza geografica dei sintomi tipici del COVID-19 nella popolazione adulta potrebbe essere rilevante per l'identificazione di futuri focolai epidemici. I sintomi nei familiari di casi confermati di COVID-19 potrebbero aiutare a identificare la diffusione intrafamiliare del virus e la sua ulteriore propagazione nella comunità. In particolare, la febbre bassa è frequente nei bambini con almeno un membro della famiglia con COVID-19 e probabilmente indica un'infezione infantile.

Parole chiave: COVID-19, SARS-CoV-2, sintomi, Italia, NINFEA

What is already known

- A number of cases positive for SARS-CoV-2 escape surveillance systems, especially in the first epidemic waves and/or when the number of cases becomes too large to allow complete diagnostic coverage.

- Some web-based surveys have been launched to explore the population prevalence of COVID-19-like symptoms, but these surveys, generally based on volunteers, have no information on the response proportion, and are, thus, prone to selection bias when aiming to estimate the population prevalence.

What this study adds

- In the 6-8 weeks since the first known autochthonous Italian COVID-19 case, more than a half of the interviewed families had at least one family member with at least one COVID-19-like symptom.

- There is a strong correlation between the prevalence of muscle pain, fatigue, low-grade fever and breathing difficulties in adults and the population cumulative number of SARS-CoV-2 cases.

- There is a clear pattern of familiar symptom aggregation among adults with at least one family member diagnosed with COVID-19, while in children, exposure to COVID-19 within the family is associated with a strongly increased prevalence of low-grade fever and anosmia/dysgeusia, but with no other symptoms

Introduction

It is recognized that a substantial number of cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) remain undiagnosed, escaping surveillance systems. These mainly include asymptomatic individuals and patients with mild or subclinical presentations that likely represent the majority of patients, especially among children [1, 2]. Reported symptoms of coronavirus disease 2019 (COVID-19) include fever, cough, sore throat, shortness of breath, myalgia, fatigue, diarrhoea, nausea or vomiting, and headache [3, 4]. In particular, loss of smell (anosmia) and taste (dysgeusia) have been reported to be highly suggestive of SARS-CoV-2 infection [5, 6].

Even if symptoms of COVID-19 play an important role in seeking health care assistance or self-isolation and informing the testing and diagnostic workflow [7], their population-based prevalence has been less investigated. Likewise, it is unclear whether this prevalence may inform on the spread of the disease beyond surveillance systems. This is particularly true in children, who rarely have a severe form of the disease, and are thus seldom tested for SARS-CoV-2 outside the investigation of clusters, for example at schools. As a consequence, children represent a rather small proportion of all reported diagnosed COVID-19 cases (e.g. children 0-9 years 3.2% in Italy as of October 27th 2020) [8]; but may play an important role in the spread of the disease and contribute to herd immunity. Based on the preliminary results of an Italian national seroprevalence study conducted in May – June 2020 [9], it can be estimated that in the age group 0-19 years out of 100 cases only 2.5 were actually diagnosed, while the same estimate in adults (≥20 years) was 18.9%.

Some web-based surveys have been launched to explore, among other aims, the population prevalence of COVID-19-like symptoms. Many of these surveys, however, recruit volunteers online with no information on the response proportion. Thus they are prone to selection bias when aiming to estimate the population prevalence, as individuals with specific symptoms, or who experienced those symptoms in the recent past, may be more or less likely to volunteer than asymptomatic individuals. Additionally, some ad-hoc web-based cohorts have been established, in which participants volunteer to report their symptoms on a regular basis [10]. This design is less affected by selection bias as participants may be enrolled before the onset of the symptoms.

The first confirmed autochthonous COVID-19 case in Italy was identified on February 21, 2020. To explore the relationship between reported COVID-19-like symptoms and the registered COVID-19 diagnoses in children and adults during the first epidemic wave in Italy, on April 7th, we invited the participants of an Italian NINFEA (Nascita e Infanzia: gli Effetti dell'Ambiente; Birth and Childhood: Effects of the Environment) birth cohort involving women recruited during pregnancy between 2005 and 2016 and their families to complete a short online questionnaire on COVID-19, with a particular focus on symptoms. The questionnaire closed on April 20th, after 13 days. In this paper, we (i) explore the geographical correlation between the population prevalence of COVID-19-like symptoms in the adults and children of the cohort during the initial phases of the epidemic and the cumulative number of new SARS-CoV-2 positive cases reported by the Surveillance System; (ii) analyse the clustering of symptoms within families with or without a member who tested negative for SARS-CoV-2 or was diagnosed with COVID-19; and (iii) estimate the sensitivity, positive and negative predictive values for COVID-19-like symptoms in the tested individuals of the NINFEA population.

Methods

Study design and population

The NINFEA study is an Italian internet-based mother-child cohort (www.progettoninfea.it) set up to investigate the influence of early-life exposures on later childhood and adulthood health. Between 2005 and 2016, approximately 7,500 pregnant women were recruited by completing the baseline questionnaire, and the children are currently followed up with questionnaires completed by mothers at 6 and 18 months after delivery and when the children turn 4, 7, 10 and 13 years. Details on the cohort have been published before [11-14].

The NINFEA study was approved by the Ethical Committee of the San Giovanni Battista Hospital and CTO/CRF/Maria Adelaide Hospital of Turin (project number 45). Parental consent (written web-based) was obtained at enrolment, after completing each study follow-up questionnaire, and additional parental written consent was obtained at the moment of biological samples collection. A specific amendment to the Ethical Committee was submitted for the COVID-19 survey, and although survey was anonymous, an online informed consent was anyhow obtained by the participants who filled in the questionnaire.

COVID-19 survey

Women who completed at least the first NINFEA follow-up questionnaire (when the child was 6 months old, N=5879) were invited to complete an anonymous online questionnaire to assess the prevalence of COVID-19-like symptoms in their households. A first e-mail was sent out on April 7, 2020, approximately 5 weeks after the Italian government imposed national lockdown. The questionnaire remained open for 13 days (until April 20th) and, during this period, two reminder e-mails were sent.

The questionnaire consisted of background information on respondents' age, sex, year of recruitment into the NINFEA cohort, educational level, province, region and area of residence, and the source from which information on COVID-19 was sought. The second part of the questionnaire asked about family composition and sex and age of family members; and included a checklist of COVID-19-like symptoms since the day of the first reported case in Italy (February 21, 2020), and in the last week, for each close family member (mother, partner, and each child <18 years old). The symptoms included: nasal congestion, low-grade fever (37.0-37.5°C), fever (>37.5°C), cough, sore throat, nausea/vomiting, diarrhea, muscle pain, and fatigue. Questions on breathing difficulties and loss of smell or taste (anosmia/dysgeusia) were introduced a few days after launching the questionnaire, and are available for 64.2% of the respondents. We also collected information on SARS-CoV-2 testing (using nasopharyngeal swabs and real-time reverse transcription polymerase chain reaction [RT-PCR]) and COVID-19 diagnosis for each of the close family members and other people living in the same household. An English version of the questionnaire is provided in **Additional File 1**.

Administrative data

The population cumulative incidence of new SARS-CoV-2 positive cases until April 7, 2020 by province was obtained from national Surveillance System data available at the website of the

Italian Ministry of Health/Civil Protection Department [15] and province population size (all residents as of January 1, 2020) obtained from the Italian National Institute of Statistics [16].

Statistical analyses

To account for survey non-response, weights for each respondent were calculated using iterative proportional fitting [17], allowing the distribution of the survey variables to closely resemble the known NINFEA population margins. The weights were calculated using the following maternal characteristics: age (<35 years, 35-40 years, 40-45 years, 45-50 years and ≥50 years), educational level (low - primary school or less, medium - secondary school, and high - university degree or higher), and period of enrolment in the NINFEA study (2005-2008, 2009-2012, 2013-2016).

Using the estimated weights, descriptive statistics were calculated for sociodemographic characteristics, cumulative symptoms, SARS-CoV-2 testing and COVID-19 diagnosis separately for children <6 years, children 6-11 years, adolescents (12-17 years) and adults.

To explore the geographical correlation between the prevalence of COVID-19-like symptoms and the population cumulative number of newly reported SARS-CoV-2 cases, we first estimated the predicted probability of each symptom given the province of residence using weighted logistic regression models and accounting for family clusters. These analyses were performed only in provinces with more than 50 study subjects (Alessandria, Asti, Cuneo and Torino, in Piedmont; Milan, in Lombardy; Arezzo, Lucca, and Florence, in Tuscany; Rome, in Lazio). The predicted probabilities were correlated to the corresponding province cumulative incidences per 1000 inhabitants (as of April 7, 2020), using Spearman's rank correlation coefficients. These analyses were performed separately in children (<6 years, 6-11 years, and 12-17 years), in adults, and at the household-level.

To analyse the clustering of symptoms within families exposed to SARS-CoV-2 we used a three-level exposure variable defined as: i) no family/household member tested for SARS-CoV-2, ii) at least one tested member but none with COVID-19, and iii) at least one member being diagnosed with COVID-19. This exposure was analysed in association with the presence of each COVID-19-like symptom, separately in children (0-17 years) and in adults. We estimated the prevalence ratios, with corresponding 95% confidence intervals (CIs), using weighted Poisson regression models with cluster-robust standard errors to account for the family structure. Models were adjusted for sex, age, maternal educational level (low, medium, high), family size (2 members, 3 members, 4 members, and ≥5 members), area of residence (urban, suburban, and rural), region of residence (Piedmont, Tuscany, Lombardy, other regions of Northern Italy, Central Italian regions, Southern Italian regions, and abroad), and maternal age (for analysis of children). Two sensitivity analyses were performed: i) excluding all reported COVID-19 cases in the analyses based on adults, and ii) considering only children older than 6 years of age in the analyses based on children. Further stratification by child age group was not possible due to small number of exposed cases.

For each symptom, we calculated its sensitivity for COVID-19 among NINFEA adults and its positive (PPV) and negative (NPV) predictive values among NINFEA adults tested for SARS-CoV-2. As more than 60% of the NINFEA participants come from Piedmont, one of the Italian regions most affected by COVID-19, we repeated the analyses restricted to Piedmont residents. For these, we also estimated the population PPV of each symptom.

All analyses were conducted using Stata version 15.1 (College Station, Texas, USA).

Results

The descriptive characteristics of the study population are shown in **Table 1.** A total of 3184 NINFEA participants responded to the COVID-19 survey, 54.2% of the total population invited. Their characteristics, including age, region of residence and year of enrolment in the NINFEA cohort were similar to those of the NINFEA cohort at baseline. Information was collected on 3184 households, 6133 adults, and 5751 children.

Table 1. Descriptive statistics of the study population / Tabella 1. Statistiche descrittive della popolazione in studio

Characteristics		N[a]	Weighted prevalence (95% CI) / Weighted mean (SD)[b]
Total number of families		3184	/
Total number parents		6133	/
Total number of children (<18 years)		5751	/
Sex (parents)			
	Female	3178	51.9 (51.6; 52.2)
	Male	2955	48.1 (47.8; 48.4)
Single parent			
	Yes	235	7.6 (6.7; 8.6)
	No	2949	92.4 (91.4; 93.3)
Sex (children)			
	Female	2788	48.9 (47.6; 50.2)
	Male	2917	51.1 (49.8; 52.4)
Maternal age		3169	41.9 (5.0)
	<35 years	201	7.4 (6.5; 8,5)
	35-40 years	746	24.1 (22,6; 25,6)
	40-45 years	1160	36.8 (35,1; 38,5)
	45-50 years	839	25.5 (24,1; 27,1)
	≥50 years	223	6.2 (5,4; 7,0)
Paternal age		2931	44.6 (6.1)
	<35 years	106	4.0 (3.3; 4.8)
	35-40 years	440	15.5 (14.2; 16.9)
	40-45 years	911	31.3 (29.6; 33.0)
	45-50 years	894	30.4 (28.7; 32.1)
	≥50 years	580	18.9 (17.5; 20.3)
Child age		5735	7.7 (3.7)
	<6 years	1671	29.0 (27.7; 30.3)
	6-11 years	3096	54.7 (53.4; 55.9)
	12-17 years	968	16.3 (15.3; 17.4)
Maternal educational level[c]			
	Low	94	4.8 (4.0; 5.9)
	Medium	948	33.3 (31.7; 35.1)
	High	2128	61.9 (60.1; 63.6)
Family size			
	2 members	118	3.8 (3.2; 4.5)

3 members	875	27.0 (25.5; 28.6)
4 members	1629	51.5 (49.4; 52.9)
≥ 5 members	562	18.1 (16.8; 19.5)
Number of children <18 years in the household		
1 child	1032	32.0 (30.4; 33.7)
2 children	1808	56.8 (55.1; 58.6)
3 children	289	9.4 (8.4; 10.5)
4 children	55	1.8 (1.4; 2.3)
Residential area		
Urban	995	30.3 (28.7; 31.9)
Suburban	1501	47.8 (46.0; 49.5)
Rural	687	21.9 (20.5; 23.4)
Region of residence		
Piedmont	2055	64.0 (62.3; 65.7)
Tuscany	640	20.6 (19.2; 22.0)
Lombardy	141	4.43 (3.8; 5.2)
Other regions of Northern Italy	160	5.2 (4.4; 6.0)
Central Italian regions	85	2.6 (2.1; 3.3)
Southern Italian regions	77	2.5 (2.0; 3.1)
Abroad	26	0.8 (0.5; 1.1)

CI = Confidence Interval / Intervalli di confidenza; SD = Standard Deviation / Deviazione standard

[a] Total numbers may vary due to missing data / I numeri totali possono variare a causa di dati mancanti

[2] Weighted for maternal age, educational level and year of the NINFEA cohort enrolment / Pesato per l'età materna, il livello di istruzione e l'anno di reclutamento

[3] Low - primary school or less, medium - secondary school, high - university degree or higher / Basso - scuola primaria o inferiore, medio - scuola secondaria, alto - laurea o superiore

Table 2 reports the weighted prevalence of COVID-19-like symptoms during the study period, separately for children aged <6 years, children aged 6-11 years, adolescents (12-17 years), adults, and at the household level. More than half of the families (55.4%) had at least one member with at least one COVID-19-like symptom. The most prevalent symptoms in adults were: fatigue (16.5%), sore throat (14.5%), cough (13.8%), nasal congestion (13.2%), and muscle pain (11.4%). Among children, the most common symptoms were nasal congestion, cough, and fever >37.5°C, and additionally sore throat and fatigue in adolescents. There was no evidence of an association between time to response and the prevalence of symptoms in adults or children (all p-values>0.05).

A total of 169 (2.6%) adults and 14 (0.2%) children were tested for SARS-CoV-2 using nasopharyngeal swabs. Twenty-eight adults (16.6%) tested positive and 2 additional subjects reported COVID-19 diagnosis without RT-PCR COVID-19 test. No information was available on diagnostic criteria for these two subjects. Thus, a total of 30 NINFEA adults (0.5%), 20 females and 10 males, were diagnosed with COVID-19. Among children, only one 5-year-old child, with both parents positive, tested positive for COVID-19.

Table 2. COVID-19-like symptoms in the 6 weeks after February 21st, 2020, in the NINFEA population / Tabella 2. Sintomi tipici del COVID-19 nella popolazione NINFEA nelle 6 settimane dopo il 21 febbraio 2020

Symptoms / COVID-19 test and diagnosis	Children <6 years N=1671		Children 6-11 years N=3096		Adolescents 12-17 years N=968		Adults N=6133		At least one family member N=3184	
	N	Weighted prevalence (95% CI)	N	Weighted prevalence (95% CI)	N	Weighted prevalence (95% CI)	N	Weighted prevalence (95% CI)	N	Weighted prevalence (95% CI)
Nasal congestion	252	14.9 (13.1; 17.0)	305	9.7 (8.6; 10.9)	67	6.7 (5.2; 8.6)	809	13.2 (12.2; 14.2)	831	26.0 (24.4; 27.5)
Fever 37.0-37.5°C	80	4.7 (3.7; 6.0)	103	3.3 (2.7; 4.1)	44	4.3 (3.1; 5.9)	397	6.6 (5.9; 7.3)	450	14.2 (13.0; 15.5)
Fever >37.5°C	189	11.1 (9.6; 12.9)	242	7.7 (6.7; 8.8)	57	5.9 (4.4; 7.9)	349	5.7 (5.1; 6.4)	561	17.6 (16.3; 19.0)
Sore throat	94	5.7 (4.5; 7.0)	202	6.5 (5.5; 7.5)	76	7.8 (6.1; 9.8)	892	14.5 (13.5; 15.6)	836	26.2 (24.6; 27.7)
Cough	242	14.4 (12.6; 16.5)	271	8.8 (7.8; 10.0)	80	8.2 (6.5; 10.3)	843	13.8 (12.8; 15.8)	889	27.9 (26.4; 30.0)
Muscle pain	32	1.9 (1.3; 2.7)	107	3.5 (2.8; 4.3)	43	4.5 (3.2; 6.2)	700	11.4 (10.5; 12.4)	597	18.8 (17.4; 20.2)
Fatigue	71	4.1 (3.2; 5.3)	161	5.1 (4.3; 6.1)	69	7.0 (5.4; 8.9)	1020	16.5 (15.4; 17.6)	818	25.5 (24.0; 27.1)
Nausea/Vomiting	45	2.5 (1.9; 3.4)	107	3.4 (2.7; 4.1)	24	2.4 (1.6; 3.6)	178	2.9 (2.5; 3.4)	278	8.7 (7.8; 9.7)
Diarrhea	88	5.1 (4.0; 6.3)	151	4.8 (4.0; 5.6)	51	4.8 (3.6; 6.4)	419	6.8 (6.1; 7.6)	473	14.8 (13.6; 16.1)
Anosmia/Dysgeusia[a]	3	0.3 (0.1; 0.8)	4	0.2 (0.1; 0.6)	5	0.8 (0.2; 2.5)	95	2.4 (1.9; 3.0)	86	4.1 (3.3; 5.1)
Breathing difficulties[a]	9	0.8 (0.4; 1.5)	11	0.6 (0.3; 1.0)	7	1.3 (0.6; 2.8)	101	2.6 (2.1; 3.2)	104	5.2 (4.3; 6.3)
At least one symptom[b]	491	28.9 (26.5; 31.5)	743	23.7 (22.1; 25.4)	230	23.1 (20.3; 26.2)	2275	37.0 (35.5; 38.5)	1773	55.4 (53.7; 57,2)
SARS-CoV-2 test[c]	2	0.1 (0.0; 0.4)	9	0.3 (0.2; 0.5)	3	0.3 (0.1; 1.0)	169	2.6 (2.2; 3.1)	164	4.9 (4.2; 5.7)
COVID-19 diagnosis	1	0.1 (0.0; 0.4)	0	/	0	/	30	0.5 (0.3; 0.7)	27	0.8 (0.6; 1.2)

CI = Confidence Interval / Intervallo di confidenza

[a] Based on 1128 children <6 years, 1955 children 6-11 years, 576 children 12-17 years, 3938 adults and 2044 families / Basato su 1128 bambini <6 anni, 1955 bambini 6-11 anni, 576 bambini 12-17 anni, 3938 adulti e 2044 famiglie

[b] Excluding anosmia/dysgeusia and breathing difficulties / Escludendo anosmia/disgeusia e difficoltà respiratorie

[c] Nasopharyngeal swabs for SARS-CoV-2 testing / Tampone rinofaringeo per test di SARS-CoV-2

Geographical correlation between population COVID-19 incidence and prevalence of COVID-19-like symptoms, testing for SARS-CoV-2 and COVID-19 diagnosis in the NINFEA population

We observed a strong geographical correlation between the population cumulative incidence of SARS-CoV-2 cases as of April 7th 2020 and the prevalence of COVID-19 diagnosis among NINFEA participants (Spearman's rho 0.80, based only on 4 provinces), and a low correlation with SARS-CoV-2 testing prevalence (**Table 3**, **Additional File 2, Figure A1**).

There was a high correlation between the population SARS-CoV-2 cumulative incidence and the prevalence of muscle pain, fatigue, low-grade fever and breathing difficulties in the NINFEA adult population, especially in men (all Spearman's rho ≥0.70, **Table 3**, **Additional File 2, Figures A2**, and **Table A1** for analyses stratified by sex). There was no clear evidence of correlation in children, apart from muscle pain across all age groups and fatigue in older children and adolescents (**Table 3**). Adolescent low-grade fever was also correlated with the population SARS-CoV-2 cumulative incidence.

Clustering of COVID-19-like symptoms within families that tested negative for SARS-CoV-2 and families diagnosed with COVID-19

We found an adjusted prevalence ratio of low-grade fever of 4.54 (95% CI: 2.20; 9.40) for children having at least one family member with a COVID-19 diagnosis, compared with children with no family members tested for SARS-CoV-2. There was also a high prevalence ratio of anosmia/dysgeusia (24.5; 95% CI: 3.47; 172.9), based only on 2 exposed cases. Similar findings were observed when the population was restricted only to children older than 6 years of age (**Additional File 2, Table A2**). There was no clear evidence of association with other symptoms (**Table 4**), including muscle pain and fatigue, the only symptoms in children showing a high ecological (province-level) correlation with the population SARS-CoV-2 cumulative incidence. However, muscle pain and fatigue in children were strongly associated with muscle pain and fatigue in their parents (data not shown), suggesting that these may just be proxies of the same symptoms in parents.

We found increased prevalence ratios of almost all COVID-19-like symptoms when comparing adults with at least one family member with a COVID-19 diagnosis with those whose household members were not tested for SARS-CoV-2 (**Table 4**). Particularly high prevalence ratios were found for breathing difficulties (14.4; 95% CI: 7.98; 26.0), anosmia/dysgeusia (13.64; 95% CI: 7.34; 25.4), and fever >37.5°C (8.68; 95% CI: 6.10; 12.3). Most of these associations remained after we excluded all reported COVID-19 cases to assess whether the observed prevalence ratios were due to the positive COVID-19 family member(s) (**Table 4**, last row).

Increased prevalence ratios, although of a lower magnitude, were observed when comparing adults with at least one family member who tested negative for SARS-COV-2 with adults from untested households. In children, conversely, having a family member who tested negative for SARS-CoV-2 was not associated with an increased prevalence of any of the symptoms.

Table 3. Geographical correlation between SARS-CoV-2 population cumulative incidence and COVID-19-like symptoms, testing and diagnosis in the NINFEA population / Tabella 3. Correlazione geografica tra l'incidenza cumulativa di casi di COVID-19 per provincia e sintomi, test e diagnosi di COVID-19 nella popolazione NINFEA

Symptoms / SARS-CoV-2 testing and COVID-19 diagnosis	Children <6 years		Children 6-11 years		Adolescents 12-17 years		Adults		At least one family member	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Nasal congestion	-0.05	0.91	-0.08	0.83	-0.11	0.82	0.30	0.43	0.10	0.80
Fever 37.0-37.5°C	-0.33	0.42	-0.08	0.83	**0.77**	0.07	**0.74**	0.04	0.22	0.58
Fever >37.5°C	0.02	0.97	0.15	0.70	0.03	0.96	0.37	0.33	0.13	0.73
Sore throat	0.14	0.74	0.25	0.52	0.69	0.06	0.47	0.21	0.65	0.06
Cough	-0.66	0.05	0.07	0.86	0.17	0.69	0.25	0.52	-0.02	0.97
Muscle pain	**0.71**	0.07	**0.74**	0.04	**0.80**	0.20	**0.88**	0.002	**0.97**	0.00
Fatigue	0.39	0.38	**0.78**	0.01	**0.90**	0.04	**0.73**	0.02	0.65	0.06
Nausea/Vomiting	0.19	0.65	-0.10	0.82	0.30	0.62	0.12	0.77	0.38	0.31
Diarrhea	-0.09	0.82	0.25	0.52	**-0.80**	0.20	0.32	0.41	0.05	0.90
Anosmia/Dysgeusia	-0.50	0.67	/	/	/	/	0.52	0.18	0.52	0.18
Breathing difficulties	-0.50	0.67	-0.20	0.70	0.50	0.67	**0.76**	0.03	0.52	0.15
At least one symptom[a]	-0.47	0.21	0.50	0.17	-0.25	0.52	0.42	0.26	-0.30	0.43
SARS-CoV-2 test[b]	/	/	-0.30	0.62	/	/	-0.33	0.42	0.15	0.70
COVID-19 diagnosis	/	/	/	/	**/**	**/**	**0.80**	0.20	**0.80**	0.20

Provinces with at least 50 participants who responded to the NINFEA questionnaire on COVID-19 were considered: Alessandria, Asti, Arezzo, Cuneo, Florence, Lucca, Milan, Rome, and Turin. / Sono state considerate le province con almeno 50 partecipanti che hanno risposto al questionario NINFEA sul COVID-19: Alessandria, Asti, Arezzo, Cuneo, Firenze, Lucca, Milano, Roma e Torino.

Correlation coefficients of at least 0.70 are reported in bold. / In grassetto sono riportati coefficienti di correlazione di almeno 0,70.

[a] Excluding anosmia/dysgeusia and breathing difficulties / Escludendo anosmia/disgeusia e difficoltà respiratorie

[b] Nasopharyngeal swabs for SARS-CoV-2 testing / Tampone rinofaringeo per test di SARS-CoV-2

Sensitivity, PPVs and NPVs of COVID-19-like symptoms in the adult NINFEA population

Table 5 shows sensitivity, PPVs and NPVs of COVID-19 diagnosis for COVID-19-like symptoms in adults tested for SARS-CoV-2. Sensitivities higher than 70% were observed for fatigue, fever >37°C, and muscle pain (**Table 5**).

The analyses restricted to the tested NINFEA Piedmont residents revealed similar PPVs as for the full cohort, with higher PPVs for breathing difficulties (88.9%; 95% CI: 68.4; 100.0) and the loss of taste or smell (83.3%; 95% CI: 53.5; 100.0). In the entire NINFEA Piedmont population, with a COVID-19 prevalence of 0.54% (**Table 5**, last column), breathing difficulties, anosmia/dysgeusia and fever >37°C had the highest PPVs (10.8%, 7.7%, and 7.3%, respectively).

Table 4. Adjusted prevalence ratios and 95% confidence intervals of selected symptoms for negative SARS-CoV-2 testing and COVID-19 diagnosis within the family / Tabella 4. Rapporti di prevalenza aggiustati e i rispettivi intervalli di confidenza al 95% per il test SARS-CoV-2 negativo e la diagnosi di COVID-19 all'interno della famiglia

SARS-CoV-2 test[a] / COVID-19 diagnosis	Nasal congestion	Fever 37-37.5°C	Fever >37.5°C	Sore throat	Cough	Muscle pain	Fatigue	Nausea/ Vomiting	Diarrhea	Anosmia/ Dysgeusia[b]	Breathing difficulties[b]	At least one symptom[c]
CHILDREN (N=5667)[d]												
No family member tested N=5372 (94.8%)	*1.00 (reference)*											
At least one tested[a] family member but none with COVID-19 N=244 (4.3%)	0.86 (0.55; 1.34)	1.28 (0.65; 2.54)	1.26 (0.86; 1.85)	0.83 (0.47; 1.46)	0.94 (0.59; 1.50)	1.02 (0.51; 2.05)	1.01 (0.50; 2.04)	1.23 (0.61; 2.46)	1.25 (0.74; 2.12)	/[e]	2.50 (0.71; 8.76)	0.98 (0.76; 1.27)
At least one family member with COVID-19 N=51 (0.9%)	0.57 (0.14; 2.27)[f]	4.54 (2.20; 9.40)	1.11 (0.37; 3.35)	0.62 (0.16; 2.44)[f]	0.38 (0.09; 1.53)[f]	0.56 (0.08; 3.74)[f]	1.47 (0.49; 4.37)[f]	/[e]	2.24 (0.85; 5.94)	24.50 (3.47; 172.9)[f]	/[e]	1.23 (0.73; 2.06)
ADULTS (N=6117)[g]												
No family member tested N=5795 (94.7%)	*1.00 (reference)*											
At least one tested[a] family member but none with COVID-19 N=269 (4.4%)	0.87 (0.59; 1.29)	1.26 (0.77; 2.06)	2.18 (1.47; 3.23)	1.21 (0.88; 1.66)	1.53 (1.16; 2.01)	1.17 (0.81; 1.69)	1.33 (1.00; 1.78)	1.58 (0.81; 3.06)	1.54 (1.01; 2.34)	1.62 (0.62; 4.25)	1.51 (0.61; 3.77)	1.15 (0.97; 1.37)
At least one family member with COVID-19 N=53 (0.9%)	1.45 (0.76; 2.76)	4.28 (2.44; 7.49)	8.68 (6.10; 12.3)	1.93 (1.14; 3.25)	3.58 (2.63; 4.87)	4.37 (3.20; 5.97)	3.52 (2.75; 4.50)	6.22 (3.45; 11.2)	4.52 (3.06; 6.68)	13.64 (7.34; 25.4)	14.4 (7.98; 26.0)	1.81 (1.49; 2.19)
Sensitivity analysis												
At least one family member with COVID-19 – COVID-19 cases excluded N=23 (0.4%)	0.37 (0.06; 2.50)	2.28 (0.64; 8.14)	2.44 (0.62; 9.68)	1.37 (0.48; 3.91)	2.21 (1.02; 4.81)	2.50 (1.16; 5.36)	1.99 (1.02; 3.89)	1.86 (0.26; 13.11)	3.13 (1.31; 7.53)	12.58 (4.70; 33.68)	6.55 (1.75; 24.55)	0.99 (0.54; 1.80)

[a] Nasopharyngeal swabs for SARS-CoV-2 testing / Tampone rinofaringeo per test di SARS-CoV-2

[b] Based of 3605 children and 3938 adults / Basato su 3605 bambini ≥6 anni e 3938 adulti

[c] Excluding anosmia/dysgeusia and breathing difficulties / Escludendo anosmia/disgeusia e difficoltà respiratorie

[d] Adjusted for child sex and age, maternal age and educational level, family size, residential area and region of residence / Aggiustato per sesso e ed età del bambino, età materna, livello di istruzione della madre, dimensione della famiglia, area di residenza e regione di residenza.
[e] No exposed cases / Nessun caso esposto
[f] Based on less than 5 exposed cases / Basato su meno di 5 casi esposti
[g] Adjusted for age, sex, maternal educational level, family size, residential area, and region of residence / Aggiustato per età, sesso, livello di istruzione della madre, dimensione della famiglia, area di residenza e regione di residenza.

329
330 **Table 5. Sensitivity, PPVs and NPVs of COVID-19 diagnosis for COVID-19-like symptoms in adults /** Tabella 5. Sensibilità, PPV e NPV della diagnosi
331 di COVID-19 per sintomi tipici del COVID-19 negli adulti

Symptoms[a]	Sensitivity (95% CI)[b] among NINFEA participants	PPV (95% CI)[b] among NINFEA participants tested for SARS-CoV-2[c]	NPV (95% CI)[b] among NINFEA participants tested for SARS-CoV-2[c]	PPV (95% CI)[b] among NINFEA Piedmont residents tested for SARS-CoV-2[c]	PPV (95% CI)[b] among NINFEA Piedmont residents
Nasal congestion	30.0% (13.6; 46.4)	32.1% (14.8; 49.4)	86.5% (80.9; 92.2)	36.8% (15.2; 58.5)	1.4% (0.4; 2.4)
Fever 37.0-37.5°C	36.7% (19.4; 53.9)	40.7% (22.2; 59.3)	88.0% (82.7; 93.4)	47.1% (23.3; 70.8)	3.1% (1.0; 5.3)
Fever >37.5°C	70.0% (53.6; 86.4)	44.4% (29.9; 59.0)	93.5% (89.2; 97.9)	51.7% (33.5; 69.9)	7.3% (3.9; 10.8)
Sore throat	36.7% (19.4; 53.9)	26.8% (13.3; 40.4)	86.7% (80.8; 92.6)	32.1% (14.8; 49.4)	1.5% (0.5; 2.5)
Cough	60.0% (42.5; 77.5)	32.1% (19.9; 44.4)	91.2% (85.9; 96.4)	36.8% (21.5; 52.2)	2.6% (1.3; 4.0)
Muscle pain	70.0% (53.6; 86.4)	42.9% (29.0; 56.7)	94.2% (90.0; 98.4)	55.2% (37.1; 73.3)	3.6% (1.9; 5.4)
Fatigue	80.0% (65.7; 94.3)	36.5% (24.6; 48.4)	95.3% (91.2; 99.3)	43.9% (28.7; 59.1)	2.9% (1.6; 4.2)
Nausea/Vomiting	30.0% (13.6; 46.4)	60.0% (35.2; 84.8)	87.7% (82.5; 92.9)	60.0% (29.6; 90.4)	5.4% (1.2; 9.6)
Diarrhea	40.0% (22.5; 57.5)	35.5% (18.6; 52.3)	87.7% (82.2; 93.2)	40.0% (18.5; 61.5)	3.1% (1.0; 5.1)
Anosmia/Dysgeusia	42.9% (16.9; 68.8)	50.0% (19.0; 81.0)	91.6% (86.0; 97.2)	83.3% (53.5; 100.0)	7.7% (1.2; 14.2)
Breathing difficulties	57.1% (31.2; 83.1)	61.5% (35.1; 88.0)	94.6% (89.9; 99.2)	88.9% (68.4; 100.0)	10.8% (3.7; 17.9)
Estimated a priori COVID-19 prevalence	/	16.6%	16.6%	18.5%	0.54%

[a] Based on 6133 NINFEA participants (3948 among Piedmont residents) for all symptoms but anosmia/dysgeusia and breathing difficulties which estimates are based on 3938 NINFEA participants (2552 from Piedmont). / Basato su 6133 partecipanti NINFEA (3948 tra i residenti in Piemonte) per tutti i sintomi tranne anosmia/disgeusia e difficoltà respiratorie le cui stime sono basate su 3938 partecipanti NINFEA (2552 residenti in Piemonte).
[b] Wald binomial confidence intervals / Intervalli di confidenza binomiali di Wald
[c] Nasopharyngeal swabs for SARS-CoV-2 testing / Tampone rinofaringeo per test di SARS-CoV-2

Discussion

We used data obtained from the members of an ongoing cohort of Italian children and their family members, mainly from northern Italy, to study COVID-19-like symptoms in children and adults during the initial phases of the COVID-19 epidemic. In the 6-8 weeks since the first known autochthonous Italian COVID-19 case, more than a half of the interviewed families had at least one family member with at least one COVID-19-like symptom. Overall, adults reported a relatively high prevalence of fatigue, cough, sore throat, nasal congestion and muscle pain, while in children the most frequent symptoms included nasal congestion, cough and fever. While COVID-19-like symptoms were quite frequent, the prevalence of diagnosed COVID-19 in the cohort was 0.5% among adults, close to 0% among children, and 16.6% among adults tested for SARS-COV-2. This may suggest that COVID-19-like symptoms are in general not highly specific and/or that SARS-CoV-2 infection is underdiagnosed, especially in children. These two aspects were further explored in our study at an ecological and individual level.

Ecologically, there was a strong correlation between the prevalence of muscle pain, fatigue, low-grade fever and breathing difficulties in adults and the population cumulative number of SARS-CoV-2 cases. In children, a similar geographical correlation was found only for the prevalence of muscle pain and fatigue, which were likely driven by parental symptoms and possible differential reporting (i.e. parents with muscle pain more likely report muscle pain in their children). Consistent with other studies [6, 10, 18, 19], our findings suggest that monitoring the prevalence of COVID-19-like symptoms in adults, but not in children, may serve as an alert of changes in disease activity and may inform about local disease clusters.

It has been reported that most COVID-19 cases had either documented contact with an infected case or were part of family clusters [4, 20-23]. In a report based on 171 COVID-19-positive children, 90.1% of cases came from COVID-19 positive families [4]. Here, we examined the prevalence of COVID-19-like symptoms in the presence of a family member with COVID-19. In children, exposure to COVID-19 within the family was associated with a strongly increased prevalence of low-grade fever (37.0-37.5°C) and anosmia/dysgeusia, but with no other symptoms. This is consistent with previous findings that children are often asymptomatic [4, 24-25], but, when they are symptomatic, fever is the most frequent symptom, with a reported prevalence between 40% and 56% [4, 25-28]. It is possible that children from COVID-19 positive families have a mild presentation of the disease without receiving diagnosis and escaping the surveillance systems. Additionally, our finding was confined to low-grade fever, suggesting that in children low-grade fever may be more specific to SARS-CoV-2 infection than fever above 37.5°C.

On the other hand, the analyses in adults showed a clear pattern of familiar symptom aggregation. Adults in households with at least one family member diagnosed with COVID-19 had a higher prevalence of almost all symptoms compared with adults with no family member tested for SARS-CoV-2. The same symptoms were also associated with SARS-CoV-2 negative testing in the household, suggesting that testing was also performed for symptoms caused by infectious diseases other than COVID-19. The most relevant symptoms in adults exposed to COVID-19 within the family included breathing difficulties, anosmia/dysgeusia, muscle pain, fatigue, cough and diarrhea. This is consistent with other studies reporting the patterns of symptoms in adults with COVID-19 [6, 25, 29, 30]. Consistent with our results,

loss of smell or taste has been reported to be one of the strongest predictors of COVID-19 [6, 30]. The presence of these symptoms among adult family members of COVID-19 cases is suggestive of COVID-19 transmission within a family, and testing of symptomatic adults, and possibly children with low fever, is a key to prevent further community transmission.

Although the presence of symptoms is one of the main indications for testing, especially when contact tracing is unable to cope with an increasing number of diagnosed cases, among tested individuals in the NINFEA population, only anosmia/dysgeusia and breathing difficulties reached a PPV above 80% (in Piedmont residents, lower in the full population), and no symptom had a PPV of at least 90%; similarly, only breathing difficulties, fatigue and muscle pain had an NPV close to 95%. Finally, PPVs for SARS-CoV-2 positive testing in the population varied between 1% and 11%, with an a priori probability of 0.5%. These PPVs are the consequence of both the local testing approach and the PPV among tested individuals. COVID-19 testing practices in Italy differ across regional jurisdictions; they changed during the different phases of the outbreak, and differ across age groups. Our estimates of sensitivity and predictive values thus depend on these contextual variables, which may detract from their generalizability to other contexts.

We surveyed the population of children and their family members who are participating in a web-based birth cohort established in 2005 and followed up for many years now. Therefore, our estimates are based on the well-known underlying population, and are less prone to selection bias due to outcome-driven participation. We had an approximately 55% response proportion to the COVID-19 survey in our study, but respondents were similar to non-respondents regarding baseline characteristics, and there was no evidence of an association between late response and the prevalence of symptoms.

Although we had no information on the temporal relationship between the onset of symptoms and diagnosis, the study period is a maximum of 6-8 weeks, and it is relatively unlikely that in such a short period, the symptoms could be due to other conditions. This is, indeed, one of the main strengths of our study which was able to focus on a relatively short time period during which the first wave of COVID-19 epidemic peaked in Italy, while the ability of the surveillance system to detect the cases was rather low due to lack of preparedness. All information collected in our study was reported by one member of the family on behalf of all members, possibly leading to misclassification. This is especially true for less severe symptoms (e.g., nasal congestion) with short duration, while we do not expect misclassification for hard variables such as SARS-CoV-2 swab testing and COVID-19 diagnosis.

Conclusions

We found that the population prevalence of certain symptoms may be relevant for the identification of future local disease clusters and that symptoms in family members of confirmed COVID-19 cases could help identify the intrafamilial spread of the virus and its further propagation in the community. Despite the high population prevalence and low specificity of most of the COVID-19-like symptoms, some of these symptoms may inform future tracing of infected individuals, especially in cases when mass or even only symptomatic individuals' swab testing is impossible.

Acknowledgements The authors are grateful to Paola Ivaldi, Sonia Barccelari, Fabio Saccona, Francesco Brunetti, Ugo Casalone, and to all the participants of the NINFEA cohort for their continuous contribution to the NINFEA cohort.

Funding The NINFEA study was partially funded by the Compagnia San Paolo Foundation, which had no role in the design of the study, collection, analysis, or interpretation of data.

Conflict of interests None declared.

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Figure A1. Scatter plots of cumulative incidence of COVID-19 by province and the prevalence of testing for SARS-CoV-2 and COVID-19 diagnosis in adults from the NINFEA cohort. Data points represent provinces with at least 50 participants who responded to the NINFEA questionnaire on COVID-19: Alessandria, Asti, Arezzo, Cuneo, Florence, Lucca, Milan, Rome, and Turin.

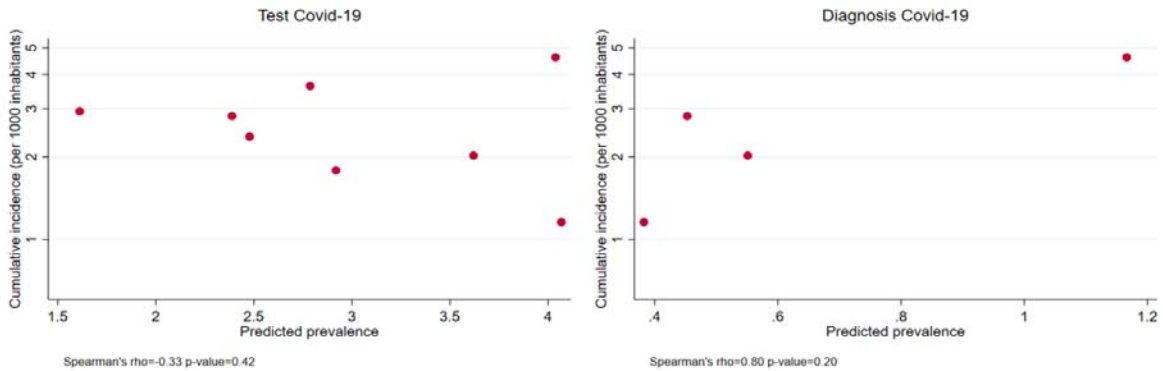

Figure A2. Scatter plots of cumulative incidence of COVID-19 by province and the prevalence of COVID-19-like symptoms in adults from the NINFEA cohort. Data points represent provinces with at least 50 participants who responded to the NINFEA questionnaire on COVID-19: Alessandria, Asti, Arezzo, Cuneo, Florence, Lucca, Milan, Rome, and Turin.

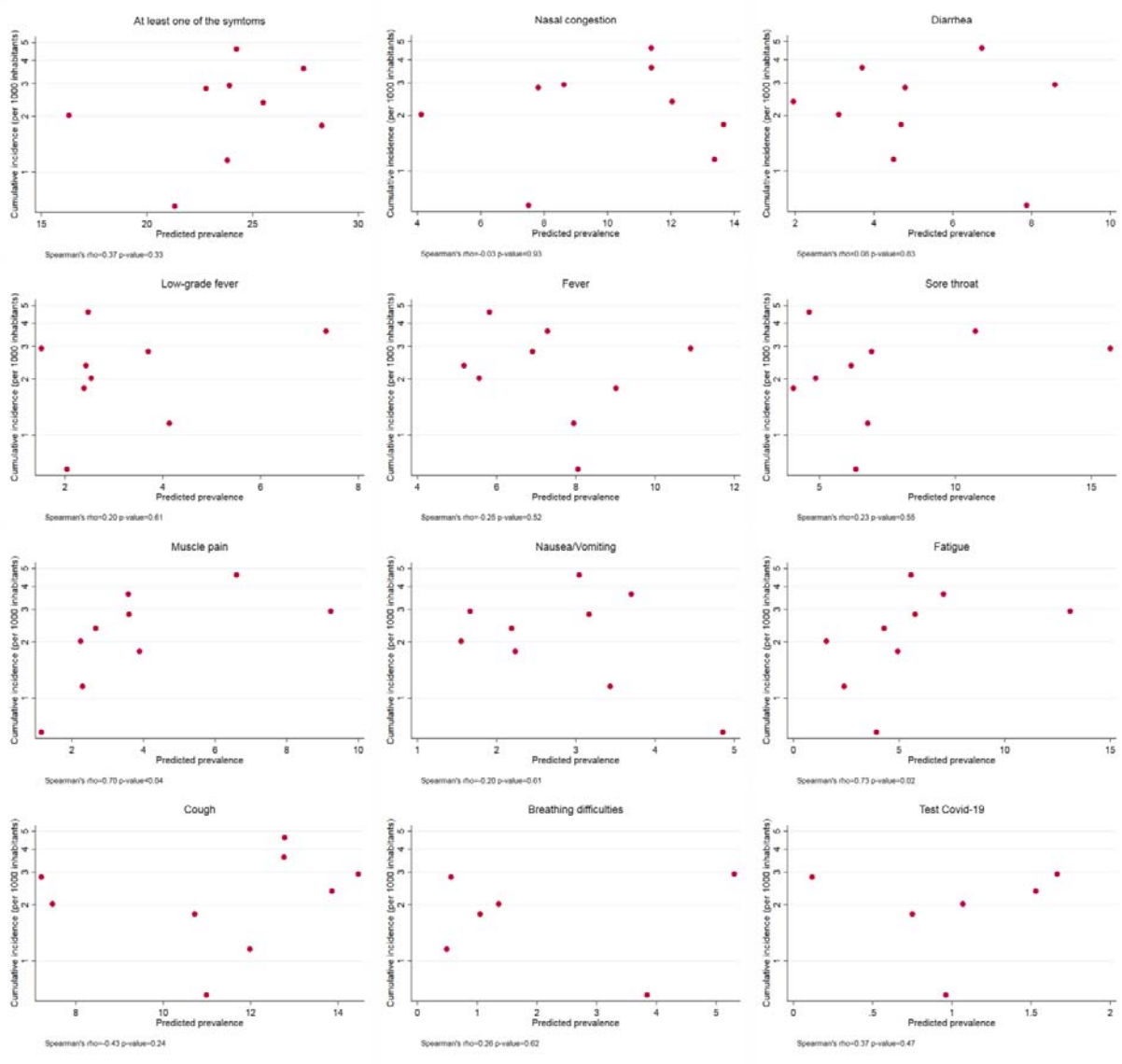

Table A1. Geographical correlation coefficients between the population cumulative incidence of COVID-19 as reported by the Surveillance System and the prevalence of COVID-19-like symptoms, testing for SARS-CoV-2 and COVID-19 diagnosis in adults from the NINFEA cohort, by sex.

Symptoms and SARS-CoV-2 testing and COVID-19 diagnosis	Females		Males	
	Spearman's rho	p-value	Spearman's rho	p-value
Nasal congestion	0.20	0.61	0.45	0.22
Fever 37.0-37.5°C	0.00	1.00	**0.95**	0.0003
Fever >37.5°C	0.50	0.17	0.17	0.67
Sore throat	0.62	0.08	0.35	0.36
Cough	0.08	0.83	0.52	0.15
Muscle pain	**0.88**	0.002	**0.93**	0.0002
Fatigue	0.62	0.08	**0.87**	0.003
Nausea/Vomiting	-0.27	0.49	0.39	0.38
Diarrhea	0.50	0.17	0.35	0.36
Anosmia/Dysgeusia	0.62	0.10	0.40	0.50
Breathing difficulties	0.60	0.12	**1.00**	0.00
At least one symptom[1]	0.27	0.49	0.57	0.11
SARS-CoV-2 test[2]	-0.45	0.26	0.33	0.42
COVID-19 diagnosis	**0.80**	0.20	0.50	0.67

Provinces with at least 50 participants who responded to the NINFEA questionnaire on COVID-19 were considered: Alessandria, Asti, Arezzo, Cuneo, Florence, Lucca, Milan, Rome, and Turin.
Correlation coefficients of at least 0.70 are reported in bold.
[1] Excluding anosmia/dysgeusia and breathing difficulties
[2] Nasopharyngeal swab for SARS-CoV-2 testing

Table A2. Adjusted prevalence ratios and 95% confidence intervals of selected symptoms for negative SARS-CoV-2 testing and COVID-19 diagnosis within the family for children 6-17 years

SARS-CoV-2 test[a] / COVID-19 diagnosis	Nasal congestion	Fever 37-37.5°C	Fever >37.5°C	Sore throat	Cough	Muscle pain	Fatigue	Nausea/ Vomiting	Diarrhea	Anosmia/ Dysgeusia[b]	Breathing difficulties[b]	At least one symptom[c]
CHILDREN 6-17 years (N=4028)[d]												
No family member tested N=3827 (95.0%)	*1.00 (reference)*											
At least one tested[a] family member but none with COVID-19 N=164 (4.1%)	0.86 (0.49; 1.50)	0.95 (0.39; 2.32)	1.50 (0.95; 2.36)	0.82 (0.44; 1.54)	0.99 (0.55; 1.79)	0.84 (0.35; 2.01)	1.02 (0.45; 2.31)	1.25 (0.58; 2.67)	1.63 (0.94; 2.81)	/[e]	2.74 (0.49; 15.21)[f]	1.00 (0.74; 1.35)
At least one family member with COVID-19 N=37 (0.9%)	0.64 (0.17; 2.47)[f]	5.27 (2.37;11.74)	0.75 (0.19; 2.95)[f]	0.79 (0.20; 3.15)[f]	0.65 (0.17; 2.55)[f]	0.69 (0.11; 4.56)[f]	0.92 (0.23; 3.66)[f]	/[e]	2.21 (0.88; 5.54)[f]	25.5 (2.58; 252)[f]	/[e]	1.24 (0.73; 2.08)

[a] Nasopharyngeal swabs for SARS-CoV-2 testing
[b] Based of 2530 children ≥6 years
[c] Excluding anosmia/dysgeusia and breathing difficulties
[d] Adjusted for child sex and age, maternal age and educational level, family size, residential area and region of residence
[e] No exposed cases
[f] Based on less than 5 exposed cases