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

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Research Article

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Abstract

Background Emerging COVID-19 pandemic caused extensive lockdowns in a number of countries, but yet unknown number of cases positive to SARS-CoV-2 escapes surveillance systems.

Methods Mothers participating in an Italian NINFEA birth cohort were invited to complete an online questionnaire on COVID-19-like symptoms in the household. We estimated the population prevalence of COVID-19-like symptoms in children and adults, assessed their geographical correlation with the cumulative number of COVID-19 cases by province, analysed their clustering within families, and estimated their sensitivity, positive (PPV) and negative predictive values (NPV) for COVID-19 diagnosis in individuals tested for SARS-CoV-2.

Results Information was collected on 3184 households, 6133 adults, and 5751 children. 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 of almost all COVID-19-like symptoms in adults, and only of low-grade fever (37-37.5°C; prevalence ratio 5.27; 95% confidence intervals: 2.37 to 11.74) and anosmia/dysgeusia in children. Among adults with COVID-19, 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%. Among tested Piedmont residents, with a COVID-19 prevalence of 18.5%, breathing difficulties and anosmia/disguesia reached PPVs above 80%.

Conclusion 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 identification of 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.

Introduction

It is recognized that a substantial, yet unknown, 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 the coronavirus disease 2019 (COVID-19) include fever, cough, sore throat, shortness of breath, myalgia, fatigue, diarrhoea, nausea or vomiting, and headache [3, 4]. Loss of smell (anosmia) and taste (dysgeusia) have also been reported as suggestive of SARS-CoV-2 infection [5, 6].

Even if symptoms of COVID-19 play an important role for people to seek health care assistance or self-isolate and to inform the testing and diagnostic workflow [7], their prevalence in the population has been little investigated. Likewise, it is not known whether this prevalence may inform on the spread of the disease in the population, 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. As a consequence, children represent a very small proportion of all reported diagnosed COVID-19 cases (e.g. 1.9% in Italy as of May 4th 2020) [8], but may play an important role in the spread of the disease and contribute to the herd immunity.

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. Also, some ad-hoc web-based cohorts have been established, in which participants volunteer to report their symptoms on a regular basis [9]. 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 Feb 21st 2020. 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) report the population prevalence of COVID-19-like symptoms in the adults and children of the cohort; (ii) explore the geographical correlation between the symptoms' prevalence and the cumulative number of new SARS-CoV-2 positive cases reported by the Surveillance System, (iii) 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, finally, (iv) estimate the sensitivity, positive and negative predictive values for COVID-19-like symptoms in 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 [10-13].

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) and all the participants gave informed consent at enrolment and after completing each study follow-up questionnaire. A specific amendment to

the Ethical Committee was submitted for the COVID-19 survey. All procedures were conducted in accordance with the relevant guidelines and regulations.

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 7th 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 respondent's 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 21st 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^{o}C), fever (>37.5^{o}C), cough, sore throat, nausea/vomiting, diarrhoea, muscle pain, and fatigue. Questions on breathing difficulties and loss of taste or smell (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 swab 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.

Administrative data

The population cumulative incidence of new SARS-CoV-2 positive cases until April 7th 2020 by province was obtained from national Surveillance System data available at the website of the Italian Ministry of Health/Civil Protection Department [14], and province population size (all residents as of January 1st 2020) obtained from the Italian National Institute of Statistics [15].

Statistical analyses

To account for survey non-response, weights for each respondent were calculated using iterative proportional fitting [16], 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 into the NINFEA study (2005-2008, 2009-2012, 2013-2016).

Using the estimated weights, descriptive statistics were calculated for socio-demographic characteristics, cumulative symptoms, SARS-CoV-2 testing and COVID-19 diagnosis separately for children <6 years, children 6-18 years, and adults.

To explore the geographical correlation between the prevalence of COVID-19-like symptoms and the population cumulative number of new 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 cluster. 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 7th 2020), using Spearman's rank correlation coefficients. These analyses were performed separately in 6-18 years old children, 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 6-18 years old children and in adults. We estimated the prevalence ratios, with corresponding 95% confidence intervals (CI), 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), and region of residence (Piedmont, Tuscany, Lombardy, other regions of Northern Italy, Central Italian regions, Southern Italian regions, and abroad), and maternal age (for analysis on children). A sensitivity analysis was performed by excluding all reported COVID-19 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 most affected Italian regions by COVID-19, we repeated the analyses restricting 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 the year of enrolment into the NINFEA cohort were similar to those of the NINFEA cohort at baseline. Information was collected on 3184 households, 6133 adults, and 5751 children.

Prevalence of COVID-19-like symptoms, SARS-CoV-2 testing and COVID-19 diagnosis in the NINFEA population

Table 2 reports the weighted prevalence of COVID-19-like symptoms between the date when the first COVID-19 case in Italy (February 21st 2020) and the moment of the survey completion. 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%). The prevalence of all symptoms, both cumulative and in the last week before the survey completion was higher in females than males (**Supplementary material; Figure S1**).

Among children, 28.9% of infants and pre-schoolers (<6 years of age) and 23.6% of school-age children and adolescents (6-18 years) experienced one or more COVID-19-like symptoms. In both groups the most common symptoms were nasal congestion, cough, and fever>37.5°C. There was no evidence of association between time to response and prevalence of symptoms in adults or children either cumulatively from February 21st or in the last week (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 swab. 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.

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**, **Supplementary material Figure S2**).

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**, **Supplementary material, Figures S2** and **S3**, and **Table S1** for analyses stratified by sex). No evidence of correlation, with the exception of muscle pain and fatigue, was found in children (Table 3, **Supplementary material, Figure S4**).

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

In 6-18 years old children, we found an adjusted prevalence ratio of low-grade fever of 5.27 (95% CI: 2.37; 11.74) for having at least one family member with 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 (25.5; 95% CI: 2.58; 252), based only on 2 exposed cases. 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 that 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.

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

Sensitivities higher than 70% were observed for fatigue, fever >37°C, and muscle pain (**Table 5**). The main analyses of PPVs and NPVs were conducted among adults tested for SARS-CoV-2, in which the prevalence of COVID-19 was 16.6%. Breathing difficulties and nausea/vomiting had the highest PPVs, with point estimates close to 60%. The NPVs for fatigue, breathing difficulties, muscle pain, fever >37°C, anosmia/dysgeusia and cough were all above 90% (**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 COVID-19 prevalence of 0.54% (**Table 5**, last column), breathing difficulties, anosmia/dysgeusia and fever >37.5°C had the highest PPVs (10.8%, 7.7%, and 7.3%, respectively).

Discussion

Several studies have described the prevalence of symptoms in series of COVID-19 patients. Data on the population prevalence of COVID-19-like symptoms in adults are scarce [6, 17, 18] while population data on children are lacking. We used data obtained from the members of an on-going cohort of Italian children and their family members, mainly from the 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 half of the interviewed families had at least one family member with at least one COVID-19-like symptom. Overall, adults reported 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 an 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). Consistently with a study from the UK,[9,17] 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 a documented contact with an infected case or were part of family clusters [4, 19, 20]. In a report based on 171 COVID-19 positive children, 90.1% of cases came from COVID-19 positive families [4]. Here, we looked at 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^{o}C) and anosmia/dysgeusia, but with no other symptoms. This is consistent with previous findings that children are often asymptomatic [4, 20-22] but, when they are symptomatic, fever is the most frequent symptom, with reported prevalence among cases between 40% and 56% [4, 22-24]. 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. Also, 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 performed also for symptoms caused by other infectious diseases 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 diarrhoea. This is consistent with the patterns of symptoms described in adults with COVID-19 both in China and in the US [22, 25]. Consistently with our results, loss of smell or taste, has been reported to be one of the strongest predictors of COVID-19 in the UK population [6]. 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 key to prevent further community transmission.

It is important to understand whether the presence of symptoms in the population should guide testing approaches. Some of the symptoms considered here, including fatigue, muscle pain, fever and cough, were characterised by a high sensitivity, with values that are consistent with previous studies [22, 25]. However, among tested individuals, only anosmia/disguesia 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 a 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.

Our study is the first one to report the adult population prevalence of COVID-19-like symptoms, their familial aggregation, and their relation to SARS-COV-2 epidemic in Italy, and to our knowledge it is the first to report these estimates in children in any population. 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 for what regards baseline characteristics, and there was no evidence of association between late-response and prevalence of symptoms.

One of the limitations of our study is the lack of information on the temporal relationship between the COVID-19-like symptoms and diagnosis, as we assessed both as the prevalence between February 21st 2020 and the date of completion of the questionnaire. However, the assessed period is maximum 6-8 weeks and it is relatively unlikely that in such a short period the symptoms could be due to other conditions. All information 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 like SARS-CoV-2 swab testing and COVID-19 diagnosis.

Conclusions

Because family clusters and especially people with asymptomatic and mild disease, including children, are likely playing a role in transmission of COVID-19 in the community, their identification and preventive social distancing is essential in slowing the spread of the virus, and protecting the health care system from overloading. We found that the population prevalence of certain symptoms may be relevant for identification of future local disease clusters, and that symptoms in family members of confirmed COVID-19 cases could help identification of 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.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the conception and the design of the study. CM coordinated the acquisition of the data. MP, CM, and EI analysed the data. All authors were involved in the data interpretation. MP and LR drafted the first version of the manuscript. All authors revised the manuscript critically for important intellectual content and all have approved the version to be submitted.

Availability of data

The datasets used and analysed during the current study are available from the corresponding author on reasonable request. The number of new SARS-CoV-2 positive cases until April 7th 2020 by province was obtained from national Surveillance System data (Italian Ministry of Health/Civil Protection Department) available in the GitHub repository, https://github.com/pcm-dpc/COVID-19, while the province population size was obtained from the website of Italian National Institute of Statistics, http://dati.istat.it/.

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Tables

Table 1. Descriptive statistics of the study population

Characteristics	N[1]	Weighted prevalence (95% CI) / Weighted mean (SD)[2]
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)
6-18 years	4064	71.0 (69.7; 72.3)
Maternal educational level[3]		
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 Intervals; SD = Standard Deviation

[1] Total numbers may vary due to missing data

[2] Weighted for maternal age, educational level and year of the NINFEA cohort enrolment

[3] Low - primary school or less, medium - secondary school, high - university degree or higher

Table 2. COVID-19-like symptoms in the 6 weeks after February 21st 2020 in the NINFEA population

Symptoms / COVID-19 test and diagnosis	Children <6 years N=1671		Children ≥6 years N=4064		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)
Nasal congestion	259	14.9 (13.1; 17.0)	372	9.0 (8.1; 10.1)	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)	147	3.6 (3.0; 4.3)	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)	299	7.3 (6.4; 8.3)	349	5.7 (5.1; 6.4)	561	17.6 (16.3; 19.0)
Sore throat	94	5.7 (4.5; 7.0)	278	6.8 (5.9; 7.7)	892	14.5 (13.5; 15.6)	836	26.2 (24.6; 27.7)
Cough	242	14.4 (12.6; 16.5)	351	8.7 (7.7; 9.8)	843	13.8 (12.8; 15.8)	889	27.9 (26.4; 30.0)
Muscle pain	32	1.9 (1.3; 2.7)	150	3.7 (3.1; 4.5)	700	11.4 (10.5; 12.4)	597	18.8 (17.4; 20.2)
Fatigue	71	4.1 (3.2; 5.3)	230	5.6 (4.8; 6.5)	1020	16.5 (15.4; 17.6)	818	25.5 (24.0; 27.1)
Nausea/Vomiting	45	2.5 (1.9; 3.4)	131	3.1 (2.6; 3.8)	178	2.9 (2.5; 3.4)	278	8.7 (7.8; 9.7)
Diarrhoea	88	5.1 (4.0; 6.3)	202	4.8 (4.1; 5.6)	419	6.8 (6.1; 7.6)	473	14.8 (13.6; 16.1)
Anosmia/Dysgeusia[1]	3	0.3 (0.1; 0.8)	9	0.4 (0.2; 0.8)	95	2.4 (1.9; 3.0)	86	4.1 (3.3; 5.1)
Breathing difficulties[1]	9	0.8 (0.4; 1.5)	18	0.7 (0.4; 1.3)	101	2.6 (2.1; 3.2)	104	5.2 (4.3; 6.3)
At least one symptom[2]	491	28.9 (26.5; 31.5)	973	23.6 (22.1; 25.1)	2275	37.0 (35.5; 38.5)	1773	55.4 (53.7; 57,2)
SARS-CoV-2 test[3]	2	0.1 (0.0; 0.4)	12	0.3 (0.2; 0.5)	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	/	30	0.5 (0.3; 0.7)	27	0.8 (0.6; 1.2)

CI = Confidence Intervals

[1] Based on 1128 children <6 years, 2530 children ≥6 years, 3938 adults and 2044 families

[2]Excluding anosmia/dysgeusia and breathing difficulties

[3]Nasopharyngeal swab for SARS-CoV-2 testing

Table 3. Geographical correlation between the population cumulative incidence of SARS-CoV-2 and the prevalence of COVID-19-like symptoms, testing for SARS-CoV-2 and COVID-19 diagnosis in the NINFEA population.

Symptoms / SARS-CoV-2 testing and COVID-19 diagnosis	Children ≥6 years		Adults		At least one family member	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Nasal congestion	-0.03	0.93	0.30	0.43	0.10	0.80
Fever 37.0-37.5°C	0.20	0.61	**0.74**	0.04	0.22	0.58
Fever >37.5°C	-0.25	0.52	0.37	0.33	0.13	0.73
Sore throat	0.23	0.55	0.47	0.21	0.65	0.06
Cough	0.43	0.24	0.25	0.52	-0.02	0.97
Muscle pain	**0.70**	0.04	**0.88**	0.002	**0.97**	0.00
Fatigue	**0.73**	0.02	**0.73**	0.02	0.65	0.06
Nausea/Vomiting	-0.20	0.61	0.12	0.77	0.38	0.31
Diarrhoea	0.08	0.83	0.32	0.41	0.05	0.90
Anosmia/Dysgeusia	/	/	0.52	0.18	0.52	0.18
Breathing difficulties	0.26	0.62	**0.76**	0.03	0.52	0.15
At least one symptom[1]	0.37	0.33	0.42	0.26	-0.30	0.43
SARS-CoV-2 test[2]	0.37	0.47	-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.

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 4. Adjusted prevalence ratios and corresponding 95% confidence intervals of selected symptoms for negative SARS-CoV-2 testing[1] and COVID-19 diagnosis within the family

SARS-CoV-2 test[1] / COVID-19 diagnosis	Nasal congestion	Fever 37-37.5ºC	Fever >37.5ºC	Sore throat	Cough	Muscle pain	Fatigue	Nausea/ Vomiting	Diarrhoea	Anosmia/ Dysgeusia[2]	Breathing difficulties[2]	At le one symp
CHILDREN 6-18 years (N=4028)[4]												
No family member tested N=3827 (95.0%)	*1.00 (reference)*											
At least one tested[1] 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)	/[5]	2.74 (0.49; 15.21)[6]	1.00 (0.74 1.35)
At least one family member with COVID-19 N=37 (0.9%)	0.64 (0.17; 2.47)[6]	5.27 (2.37;11.74)	0.75 (0.19; 2.95)[6]	0.79 (0.20; 3.15)[6]	0.65 (0.17; 2.55)[6]	0.69 (0.11; 4.56)[6]	0.92 (0.23; 3.66)[6]	/[5]	2.21 (0.88; 5.54)[6]	25.5 (2.58; 252)[6]	/[5]	1.24 (0.73 2.08)
ADULTS (N=6117)[7]												
No family member tested N=5795 (94.7%)	*1.00 (reference)*											
At least one tested[1] 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)

[1] Nasopharyngeal swab for SARS-CoV-2 testing

[2] Based of 2530 children ≥6 years and 3938 adults

[3] Excluding anosmia/dysgeusia and breathing difficulties

[4] Adjusted for child sex and age, maternal age and educational level, family size, residential area and region of residence

[5] No exposed cases

[6] Based on less than 5 exposed cases

[7] Adjusted for age, sex, maternal educational level, family size, residential area, and region of residence

Table 5. Sensitivity, positive predictive values (PPVs) and negative predictive values (NPVs) of COVID-19 diagnosis for COVID-19-like symptoms in adults[1]

Symptoms	Sensitivity (95% CI)[2] among NINFEA participants	PPV (95% CI)[2] among NINFEA participants tested for SARS-CoV-2[3]	NPV (95% CI)[2] among NINFEA participants tested for SARS-CoV-2[3]	PPV (95% CI)[2] among NINFEA Piedmont residents tested for SARS-CoV-2[3]	PPV (95% CI)[2] 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 37.0-37.5ºC	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 >37.5ºC	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)
Diarrhoea	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%

[1] 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).

[2] Wald binomial confidence intervals

[3] Nasopharyngeal swab for SARS-CoV-2 testing

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