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Published on: 18 Sep 2020 - medRxiv (Cold Spring Harbor Laboratory Press)

Topics: Seroprevalence

Title

Seroprevalence of SARS-CoV-2 among adults in three regions of France following the lockdown and associated risk factors: a multicohort study.

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Key words

SARS-COV-2, COVID-19, general population, cohort, seroprevalence, risk factors

Word count

Abstract (300), text (3496), references (38), Tables (4), Figures (3) + 1 supplementary material

Abstract

Background

To estimate the seroprevalence of SARS-CoV-2 infection in May-June 2020 after the lockdown in adults living in three regions in France and to identify the associated risk factors.

Methods

Participants in a survey on COVID-19 from an existing consortium of three general adult population cohorts living in the Ile-de-France (IDF) or Grand Est (GE) - two regions with high rate of COVID-19, or in the Nouvelle-Aquitaine (NA) – with a low rate, were asked to take a dried-blood spot (DBS) for anti-SARS-CoV-2 antibodies assessment.

The primary outcome was a positive anti-SARS-CoV-2 ELISA IgG result against the spike protein of the virus (ELISA-S). The secondary outcomes were a positive ELISA IgG against the nucleocapsid protein (ELISA-NP), anti-SARS-CoV-2 neutralizing antibodies titers ≥40 (SN), and predicted positivity obtained from a multiple imputation model (MI). Prevalence estimates were adjusted using sampling weights and post-stratification methods.

Findings

Between May 4, 2020 and June 23, 2020, 16,000 participants were asked to provide DBS, and 14,628 were included in the analysis, 983 with a positive ELISA-S, 511 with a positive ELISA-NP, 424 with SN≥40 and 941±31 with a positive MI. Adjusted estimates of seroprevalence (positive ELISA-S) were 10.0% (95%CI 9.1%;10.9%) in IDF, 9.0% (95%CI 7.7%; 10.2%) in GE and 3.1% (95%CI 2.4%; 3.7%), in NA. The adjusted prevalence of positive ELISA-NP, SN and MI were 5.7%, 5.0% and 10.0% in IDF, 6.0%, 4.3% and 8.6% in GE, and 0.6%, 1.3% and 2.5% in NA, respectively.

A higher seroprevalence was observed in younger participants and when at least one child or adolescent lived in the same household. A lower seroprevalence was observed in smokers compared to non-smokers.

Interpretation

At the end of the lockdown the prevalence of anti-SARS-CoV-2 IgG or neutralizing antibodies remained low in the French adult population, even in regions with high reported rates of COVID-19.

Introduction

Serological surveys help determine the extent of infection by a viral agent in a population and identify associated risk factors.[1] In addition, characterizing the distribution of antibodies against this agent can help evaluate the portion of the population that is immunized to quantify herd immunity. However, despite the ongoing COVID-19 pandemic, there are still very few serologic surveys describing the factors associated with SARS-CoV-2 seroprevalence, and only one study explored the distribution of neutralizing antibodies against SARS-CoV-2 in a general adult population in a very low prevalence area.[2]

Serologic surveys of SARS-CoV-2 have been performed between January 2020 and July 2020 in the general population in Iceland,[3] Switzerland,[4] Spain,[5] UK,[6,7] Italy,[8] Belgium,[9] Germany,[2] China,[10] Brazil,[11] Canada,[12] and the US.[13-15] They all showed a low seroprevalence in the general population (<10%), and sometimes identified associations between a positive test result and younger age, sex, ethnicity, as well as lower socioeconomic status and population density.

In France, SARS-CoV-2 positive RT-PCR tests were first reported in imported cases on week 4 (January 24, 2020), generalized lockdown began on week 12 (March 17, 2020) and emergency room visits for possible COVID-19 peaked on week 13, decreasing thereafter. This led the French government to ease lockdown restrictions on week 20 (May 11, 2020).

Our main goals were 1) to estimate the seroprevalence of SARS-CoV-2 infection in the French adult population at the end of lockdown in three regions and 2) to identify the associated risk factors.

Participants and Methods

Design

The present report combined data collected from questionnaires in the SAPRIS ("SAnté, Perception, pratiques, Relations et Inégalités Sociales en population générale pendant la crise COVID-19") survey in France, with serological results from the SAPRIS-SERO study.

The SAPRIS survey has been described elsewhere.[16] Briefly, the survey was created in March 2020 to evaluate the main epidemiological, social and behavioral challenges of the SARS-CoV2 epidemic in France in relation to social inequalities in health and healthcare. It is based on a consortium of prospective cohort studies including three general population-based adult cohorts and two child-cohorts (not presented in this study).[17-19] All participants from the original cohorts with regular access to electronic (internet) questionnaires were invited to participate in the SAPRIS survey (supplementary figure 1). Two self-administered questionnaires covering the lockdown and the post-lockdown periods were sent as of April 1, 2020 and returned before May 27, 2020. Variables collected in the questionnaires included socio-demographics, household size and composition, COVID-19 diagnosis, SARS-CoV-2 RT-PCR test, a detailed description of the subject's symptoms in the two weeks before each questionnaire, comorbidities, healthcare use and treatment, employment, daily life, child care, alcohol, tobacco and cannabis use, social and sexual life, preventive measures, risk perception and beliefs.

The goal of the SAPRIS-SERO study (#NCT04392388) including participants enrolled in the SAPRIS survey, was to quantify and follow the cumulative incidence of SARS-CoV-2 infection in the French population using serological tests and to assess the determinants of infection. Self-sampling dried-blood spot (DBS) kits were

mailed to each participant including material (a DBS card, lancets, pad), detailed printed instructions on how to perform the test, and a self-addressed stamped padded envelope to be returned with the card to the centralized biobank (CEPH Biobank, Paris, France). Kits were received, then blood spots were visually assessed and registered in the CEPH-Biobank LIMS (BIOBASE). Four 4.7 mm discs were punched of the spots on Panthera™ (PerkinElmer) and stored in 2D FluidX 96-Format 0.5 mL tubes (Brooks) in -30°C freezers. Tubes were sent to the virology laboratory (Unité des virus Émergents, Marseille, France) for serological analysis. Eluates were processed with a commercial Elisa test (Euroimmun®, Lübeck, Germany) to detect anti-SARS-CoV-2 antibodies (IgG) directed against the S1 domain of the spike protein of the virus (ELISA-S). The volume of eluate used corresponded to the amount of serum and dilution recommended in the manufacturer's instructions. All samples with an ELISA-S test optical density ratio ≥ 0.7 were also tested with an ELISA test to detect IgG antibodies against the SARS-CoV-2 nucleocapsid protein (Euroimmun®, Lübeck, Germany, ELISA-NP) and with an in-house micro-neutralization assay to detect neutralizing anti-SARS-CoV-2 antibodies (SN), as described elsewhere.[20] Briefly, we used VeroE6 cells cultured in 96-well microplates, 100 TCID50 of the SARS-CoV-2 strain BavPat1 (courtesy of Pr. Drosten, Berlin, Germany) and serial dilutions of serum (1/20–1/160). Dilutions associated with the presence or absence of a cytopathic effect on post-infection day 4.5 were considered to be negative or positive, respectively. The neutralization titer referred to the highest dilution of positive serum. The specificity of the assay was close to 100% in a population of blood donors sampled in 2017-2018 when samples with a titer ≥40 were considered to be positive.[20]

We randomly selected 16,000 of the participants of the SAPRIS survey for this study who agreed to be tested and who were residents from one of the three French administrative regions: Ile-de-France (IDF) or Grand Est (GE), i.e. the two regions with the highest reported cumulated rates of COVID-19 at the end of the lockdown period, or Nouvelle-Aquitaine (NA), a region with a low reported rate.[21]

Ethical approval and written or electronic informed consent were obtained from each participant before enrolment in the original cohort. The SAPRIS survey was approved by the Inserm ethics committee (approval #20-672 dated March 30, 2020). The SAPRIS-SERO study was approved by the Sud-Mediterranée III ethics committee (approval #20.04.22.74247) and electronic informed consent was obtained from all participants for DBS testing.

Outcomes.

The main outcome was a positive ELISA-S test. In accordance with the manufacturer's instructions a test was considered to be ELISA-positive with an optical density ratio ≥ 1.1, ELISA-indeterminate between 0.8 and 1.1, and ELISA-negative, <0.8. The secondary outcomes were a positive ELISA-NP (using the same thresholds) and positive SN defined as a titer ≥40. Because test sensitivity and specificity was not 100%, we also used a multiple imputation (MI) method to estimate a participant's positivity in which the likelihood of positivity was based on observed test results and covariates.

Covariates

The association of seroprevalence was evaluated in relation to age, gender, socio-demographic characteristics, BMI, chronic conditions (according to a pre-specified

list), tobacco and alcohol use before the lockdown. Age groups were categorized according to predefined limits (<40; 40-49; 50-59; 60-69; ≥70 years old) and BMI according to standard cut-offs (<18.5; 18.5-<25; ≥25-<30; ≥30 kg/m^2).[22]

The association of seroprevalence was also studied in relation to symptoms. Possible COVID-19 was defined according to the European Centre for Disease Prevention and Control as at least one of the following: cough, fever, dyspnea, and sudden anosmia, ageusia or dysgeusia.[23] Participants who did not report any of these symptoms on either questionnaire, did not have a positive COVID-19 diagnosis, or did not experience cough, fever or feverishness from the beginning of the year were considered to be asymptomatic.

Statistical methods.

Inverse probability weighting and generalized raking were used to estimate seroprevalence in the adult population.[24] Weights were estimated from each cohort source by logistic regression, with selection or participation as response variables and socio-demographic characteristics as covariates. An initial cohort-specific calibration was performed by generalized raking in relation to the marginal totals of the distribution of age class, gender and socio-professional category in the target population. The weights were then rescaled according to the relative sample size of each cohort, then recalibrated according to the same covariates to provide representative estimates of the adult population. This weighting procedure was performed for each region independently. Confidence intervals for weighted estimates were computed by bootstrapping.

To fit the MI model, participants with all three positive ELISA-S, ELISA-NP and SN test results were classified as “true” positives while those with all three negative

results or ELISA-S <0.7 were “true” negatives. The Markov Chain Monte Carlo method was used to imputing MI using numerical values from the three serological tests (log-transformed), region, age and gender. The MI was built from 100 imputed data sets and estimates combined with Rubin’s rules.[25]

Chi-Square test for trend was used on unweighted data to compare symptoms and health care use according to ELISA-S results. Logistic regression models were used on unweighted data with stratification in the source cohort to identify the determinants of a positive ELISA-S (primary outcome). Indeterminate ELISA-S results were grouped with negative results in the primary analysis. Multivariable analysis was performed including region, age, gender and all factors associated with seroprevalence in univariable analysis. A backward elimination procedure was used to identify independent covariates associated with a positive ELISA-S. Contact with a RT-PCR positive household member was not considered to prevent the risk of reverse causation. Multivariable analyses were repeated using secondary outcomes then performed in each region to identify any potential regional effect-modification. Weighting and multiple imputation used the survey and mice package from R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Other analyses were performed with SAS 9·4 software (SAS Institute Inc., Cary, North Carolina, USA). P<.05 was considered to be statistically significant.

Role of the funding source

The sponsor and funders facilitated data acquisition but did not participate in the study design, analysis, interpretation or drafting. FC had full access to all data in the study and FC, XL, NB, MT, GS, MZ made the final decision to submit the study for publication.

Results

A total of 116,903 out of 279,478 (42%) adults who were invited to participate in the survey completed the 1st questionnaire and 108,595 (39%) the 2nd questionnaire (94,999 completed both) while 104,001 (80% of participants to the 1st or 2nd questionnaire) accepted the serological study (supplementary figure 1). Sixteen thousands of the 36,531 participants living in IDF, GE or NA who agreed to the serological study and had the 1st and 2nd questionnaire validated were invited to perform the DBS. The DBS was returned by 15,414 (96%) of these participants and serology was performed on 14,830 (93%) samples: 14,628 (91%) could be interpreted and were included in the analyses. The median time between the 2nd questionnaire and DBS was 12 days (Q1-Q3: 10-16 days). Ninety percent of DBS samples were performed at the end of lockdown between weeks 19 and 21 (May, 4 - May, 24 2020). Participant characteristics are described in supplementary table 1.

Seroprevalence of SARS-CoV-2

Nine hundred eighty-three participants had a positive ELISA-S, 552 in IDF, 270 in GE and 161 in NA, with weighted seroprevalence estimates in the adult population of 10.0% in IDF (95%CI 9.1%; 10.9%), 9.0% in GE (95% CI 7.7%; 10.2%) and 3.1% in NA (95% CI 2.4%; 3.7%) (table 1). The seroprevalence estimates of positive ELISA-NP and SN were markedly lower: 5.7% and 5.0%, in IDF, 6.0% and 4.3% in GE, and 0.6% and 1.3% in NA, respectively. Two hundred ninety-two participants were positive with all three methods and 13,314 were negative with all methods or had an ELISA-S <0.7, while the MI was used to predict 1,022 (supplementary figure 2): 941 participants (SD=31) were classified as MI positive, 548 (SD=23) in IDF, 259 (SD=16) in GE, 134 (SD=12) in NA, with weighted MI seroprevalence estimates in

the adult population of 10.0% in IDF (95%CI 8.9%; 11.3%), 8.6% in GE (95%CI 7.2%; 10.4%) and 2.5% in NA (95%CI 1.9%; 3.3%). The sensitivity and specificity of ELISA-S in relation to MI was 97.9% (95% CI 96.9%: 98.9%) and 97.7% (95%CI 97.4%; 98.0%), respectively. The sensitivity and specificity of ELISA-NP was 50.3% (95%CI 46.9%; 53.6%) and 99.5% (95%CI 99.3%; 99.6%), respectively, and that of SN was 41.4% (95% CI 38.2%; 44.7%) and 99.5% (95%CI 99.3%; 99.6%), respectively.

Symptoms and healthcare use

Participants with a positive ELISA-S had a higher rate of self-reported symptoms than those with negative tests except for skin lesions (table 2). Forty-seven percent of ELISA-S positive participants experienced symptoms of possible COVID-19 a median of 56 days (Q1: 40 days; Q3: 61 days) before collection of blood samples, while the rate was 24% at 53 days (46, 60) in those with indeterminate results, and 19% at 53 days (42, 61) in participants with negative results (P<0.0001). ELISA-S was positive in 74% (95%CI 64%; 84%) of participants with a positive RT-PCR test, in 47% (95%CI 43%; 51%) of those with anosmia or ageusia, in 44% (95%CI 40%; 48%) with a medical diagnosis of COVID-19, in 15% (95% CI 14%; 17%) with symptoms of possible COVID-19, and in 3.7% (95% CI 3.2%; 4.2%) of asymptomatic participants. The proportion of positive ELISA-S in participants with possible COVID-19 was higher in IDF and GE than in NA (figure 1). It also varied during lockdown and decreased from 25% in IDF (95%CI 21%; 29%), 26% in GE (95%CI 20%; 32%) and 5.3% in NA (95%CI 2.5%; 9.9%) when the onset of possible COVID-19 symptoms were reported during week 12 (March 16 - 22 – the beginning of lockdown) to 2.7% in

IDF (95%CI 0.1%; 14%), 0.0% in GE (95%CI 0%; 23%) and 2.9% in NA (0.1%; 15.3%), when the onset of symptoms was reported during week 18 (figure 1).

In participants with a positive ELISA-S, a positive ELISA-NP was found in 29/185 (16%) asymptomatic participants, in 335/454 (74%) with possible COVID-19, and in 88/319 (28%) who reported other symptoms (P<0.0001, supplementary figure 3), while a positive SN was found in 40/188 (21%), 250/459 (54%) and 81/322 (25%), respectively (P<0.0001).

Factors associated with seroprevalence

On univariable analysis, the rate of positive ELISA-S was higher in IDF and GE than in NA (table 3) as well as in younger adult groups with an observed peak in ages 35 to 44 years old in each region (figure 2). The association with age was similar with positive MI, although a higher proportion of positive SN or ELISA-NP was observed in the youngest age groups in the IDF and NA regions (supplementary figures 4&5). Multivariable analysis showed an independent and positive association between positive ELISA-S, IDF and GE compared to NA, for younger age, and at least one child or adolescent living in the same household (table 4). A negative association was found with active smoking (*vs* no smoking). The observed associations were confirmed with MI and were overall consistent with ELISA-NP and SN, although they did not all reach statistical significance due to a smaller number of events (supplementary tables 2-4). When multivariable analysis was performed in each region separately, the associations did not differ between IDF and GE but the pattern in NA was different from that in IDF or GE, with a higher Odds-Ratio (OR) in young age groups in the former (OR= 3.30 (95%CI 1.79; 6.09) in <40 *vs* [50-60] and OR= 3.89 (95%CI 2.18; 6.95) in [40-50] *vs* [50-60]) than in IDF (OR=1.80 (95%CI 1.37;

2.38) and OR=1.83 (95%CI 1.39; 2.40), respectively) and GE (OR=1.45 (95%CI 0.97; 2.17) and OR=1.44 (95%CI 0.99; 2.11), respectively). Moreover, there was a significant association with female gender in NA (OR=2.11 (95%CI 1.42; 3.14)) but not in IDF (OR= 1.00 (95%CI 0.83; 1.22)) or GE (OR=1.02 (95%CI 0.76; 1.36)) (figure 3).

Discussion

In May-June 2020 following the first wave of the COVID-19 pandemic and the subsequent lockdown in France, the seroprevalence of SARS-CoV-2-infection was 10% to 9% in the adult population in the 2 regions with the highest rate of disease and 3% in a region with a low rate. The seroprevalence of neutralizing antibody titers ≥40 or ELISA IgG against the NP protein was half that detected by ELISA IgG against the spike protein. Seroprevalence was strongly associated with reported symptoms and nearly half of the participants who tested positive experienced symptoms of COVID-19, while 1 in 5 did not recall having any symptoms. The associations between seroprevalence and age, living with at least one child or adolescent, and smoking status were consistent across all regions.

To our knowledge this is the first study evaluate the seroprevalence of SARS-CoV-2 in the general adult population in France. The rates of seroprevalence in the 3 regions were close to the cumulative proportions of infection predicted by models at the end of the lockdown period.[26] They were also in the range reported in similar studies in Europe.[4,5,7-9] Half of the participants with a positive ELISA-S had an episode corresponding to the definition of a COVID-19 case, and the reported symptoms corresponded to those described in similar studies.[5,7] One in five positive participants did not experience any symptoms from the onset of the pandemic. This was lower than in Spain[5] or England,[7] which was around 30%, perhaps due to different methods of data collection of symptoms. Interestingly, ELISA-NP and SN seroprevalence was strongly associated with the presence and intensity of symptoms in ELISA-S positive participants. These results are similar to studies suggesting that asymptomatic or paucisymptomatic individuals have a weaker immune response to SARS-CoV-2 infection.[2,27]

A lower seroprevalence with increasing age was reported in several population-based serological studies[4,6] and a higher rate of possible COVID-19 with decreasing age was described in an earlier study.[16] Although men are known to be at a higher risk of severe COVID-19, hospitalization and deaths than women,[28] we found an association between seroprevalence and female gender in NA, which was also reported in a recent Italian study.[8] This association was only found in the region with a lower prevalence and may be related to the specific dynamics of transmission in this area. Based on the estimated 5-day median COVID-19 incubation time and the appearance of symptoms within 12 days after infection,[29] participants who developed a possible COVID-19 before March 23 and tested positive were potentially infected before lockdown, probably in the workplace or in the community. This could explain why we did not find any specific association with social health inequalities, while, conversely, univariable analyses showed associations between seroprevalence and working adults with higher incomes and educational levels. As in other studies, univariable analysis identified the size of the household and the number of rooms, but only living with at least one child remained associated with seroprevalence on multivariable analysis, indicating that children could play an important role in household-related transmission.[30]

Finally, active smoking was associated with a lower rate of ELISA-S or SN positive results.[7,31] Smoking status was collected before the peak of the pandemic and thus could not have been affected by preventive behaviours in smokers. Although smoking is a risk factor for severe COVID-19 in infected patients,[32] its role in the risk of infection remains unclear because certain components of the smoke (such as nicotine) regulate ACE2 receptor expression which is involved in SARS-CoV-2 entry into cells.[33,34] Smoking is also known to be associated with lower serum levels of IgG,

IgA or IgM,[35] but this probably does not explain why smoking was also negatively correlated with SARS-CoV-2 RT-PCR positive results in several studies.[36,37]

Our study has several limitations. First, the primary endpoint is based on a test that does not have a 100% sensitivity and specificity. Thus, certain participants were probably misclassified. We used manufacturer-defined cutoff points for positivity, although the test performance can increased by using other positive and negative cut-off values.[38] However, prevalence correction using these reported test performances or by the manufacturer are not applicable to our study, since the use of capillary blood on DBS and the elution procedures do not correspond to the reported experimental conditions. To overcome this limitation, we used a statistical imputation model to estimate the performance of ELISA-S, showing a sensitivity and specificity > 97.5%. The seroprevalence levels and the risk factors identified on multivariable analysis with MI were identical to those obtained with ELISA-S, which supports the robustness of our primary results.

The second potential limitation is that the selected adult population in each region may not be representative. Certain social categories were probably under- or over-represented, and although selection and participation biases were accounted for with an appropriate weighting and raking method, our findings cannot be considered to be strictly representative of the general adult population in these regions. Nevertheless, the large number of subjects from all social categories makes it possible to draw robust conclusions on the factors associated with seroprevalence. We limited the questionnaires to detailed description of symptoms present in the past 14 days, (except for acute respiratory illness) to avoid recall bias. Thus, we may have missed symptoms related to SARS-CoV-2 infection that occurred in the last week of February when SARS-CoV-2 began spreading. On the other hand, we cannot

formally associate the self-reported COVID-19 symptoms with a positive serological result and once again, misclassification may have occurred.

This study has several strengths. In particular, it is based on well-characterized general population cohorts with a very high participation rate. Moreover, serological samples were collected within 1 to 3 months after the period of intense circulation of SARS-CoV-2 and all serological tests were centralized and performed blinded to participants' characteristics or clinical history. Several serological methods were combined, including neutralization, to improve the interpretation of seroprevalence results.

In conclusion, our study shows that the level of seroprevalence remains low in the French regions most affected by the first wave of SARS-CoV-2. Longer-term clinical and serological follow-up is needed to evaluate the duration of the humoral response, the risk of infection or re-infection, and to establish the correlates of protection - a key element in preparing for evaluation of vaccines against SARS-CoV -2.

Figure legends.

Figure 1. Proportion of participants with possible COVID-19 and a positive ELISA-S serological result according to the date of the onset of symptoms.

Figure 2. Proportion of participants with a positive ELISA-S by age (weighted estimates).

Figure 3. Risk factors of positive ELISA-S by French region.

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Acknowledgments

The authors warmly thank all the volunteers of the Constances, E3N-E4N, and NutriNet-Santé cohorts.

We thank the staff of the Constances, E3N-E4N and NutriNet-Santé cohorts that have worked with dedication and engagement to collect and manage the data used for this study and to ensure continuing communication with the cohort participants.

We thank the CEPH-Biobank staff for their adaptability and the quality of their work.

In the virology department, Dr Nadège Brisbarre and the technical staff for impeccable management of samples and serological assays.

We thank Mrs Dale Roche-Leclerc for her help in editing the manuscript.

Data Statement: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Statement: Dr Carrat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Administrative, technical, or material support: Rahib, Blanché, Lydié, Priet, Saba Villarroel, Fourié, Nicol, Legot, Druesne-Pecollo, Essedik, Lai, Gagliolo.

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Conflicts of interests:

Prof Fabrice Carrat reports personal fees from Imaxio and Sanofi, outside the submitted work.

All other authors declare no competing interest.

Funding

This study

ANR (Agence Nationale de la Recherche, #ANR-20-COVI-000, #ANR-10-COHO-06), Fondation pour la Recherche Médicale (#20RR052-00), Inserm (Institut National de la Santé et de la Recherche Médicale, #C20-26).

Cohorts funding

The CONSTANCES Cohort Study is supported by the Caisse Nationale d'Assurance Maladie (CNAM), the French Ministry of Health, the Ministry of Research, the Institut national de la santé et de la recherche médicale. CONSTANCES benefits from a grant from the French National Research Agency [grant number ANR-11-INBS-0002] and is also partly funded by MSD, AstraZeneca, Lundbeck and L'Oreal.

The E3N-E4N cohort is supported by the following institutions: Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation, INSERM, University Paris-Saclay, Gustave Roussy, the MGEN, and the French League Against Cancer. The NutriNet-Santé study is supported by the following public institutions: Ministère de la Santé, Santé Publique France, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut National de la Recherche Agronomique (INRAE), Conservatoire National des Arts et Métiers (CNAM) and Sorbonne Paris Nord. The CEPH-Biobank is supported by the « Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation ».

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Cindy Lai, Hélène Esperou, Sandrine Couffin-Cadiergues (Inserm)

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Table 1. Weighted prevalence estimates.

		ELISA-S	ELISA-NP	SN	MI
Ile-de-France (IDF) - N=6,348	number positive weighted prevalence (95% CI)	552 10.0% (9.1% ; 10.9%)	315 5.7% (4.9% ; 6.4%)	253 5.0% (4.2% ; 5.7%)	548±23 10.0% (8.9% ; 11.3%)
Grand Est (GE) - N=3,434	number positive weighted prevalence (95% CI)	270 9.0% (7.7% ; 10.2%)	161 6.0% (4.9% ; 7.0%)	120 4.3% (3.2% ; 5.2%)	259±16 8.6% (7.2% ; 10.4%)
Nouvelle-Aquitaine (NA) N=4,846	number positive weighted prevalence (95% CI)	161 3.1% (2.4% ; 3.7%)	35 0.6% (0.3% ; 0.9%)	51 1.3% (0.8% ; 1.7%)	134±12 2.5% (1.9% ; 3.3%)

Table 2. Symptoms and health care use during the survey according to ELISA-S results

	ELISA-S test result			
	Negative 13,369	Indeterminate. 276	Positive 983	P-Value (trend test)
Symptoms 1st or 2nd questionnaire				
Fever or feverishness	1,172 (9)	31 (11)	278 (28)	<0.0001
Cough	1,829 (14)	44 (16)	305 (31)	<0.0001
Dyspnea	692 (5)	20 (7)	142 (14)	<0.0001
Anosmia/ageusia	258 (2)	21 (8)	248 (25)	<0.0001
Headaches	3,851 (29)	105 (38)	451 (46)	<0.0001
Rhinorrhea	3,440 (26)	79 (29)	353 (36)	<0.0001
Fatigue	2,375 (18)	71 (26)	399 (41)	<0.0001
Stiffness, myalgia	2,138 (16)	53 (19)	300 (31)	<0.0001
Nausea	622 (5)	21 (8)	106 (11)	<0.0001
Diarrhea	1,646 (12)	43 (16)	199 (20)	<0.0001
Chest pain	1,086 (8)	31 (11)	166 (17)	<0.0001
Skin lesion (2nd Questionnaire)	384 (3)	13 (5)	39 (4)	0.4131
Did not report any symptoms in 1st and 2nd questionnaire, or cough or fever from the beginning of the year– ("asymptomatic")	4,839 (37)	86 (32)	188 (19)	<0.0001
Possible COVID-19*	2,501 (19)	67 (24)	460 (47)	<0.0001
Possible COVID-19 > 3 days	1,669 (12)	46 (17)	381 (39)	<0.0001
Delay between kit and COVID-19 - dys (median (Q1-Q3))	53 (42-61)	53 (46-60)	56 (49-61)	
Medical diagnosis of COVID-19	311 (2)	16 (6)	257 (27)	<0.0001
< March 1	21 (7)	1 (8)	1 (0)	
March, 1-16	67 (22)	4 (25)	50 (20)	
March 17-29	128 (41)	9 (56)	148 (57)	
March 30, Apr 12	66 (21)	1 (6)	50 (20)	
> Apr 12	28 (9)	1 (6)	8 (3)	
missing	301	10	28	
RT-PCR tested				
Positive/Total tested	21/164 (13)	3/7 (43)	68/78 (87)	<0.0001
NA	9	1	5	
March, 1-16	0	0	6	
March 17-29	5	1	17	
March 30, Apr 12	2	1	22	
> Apr 12	5	0	18	
Positive RT-PCR in another household member	52 (0.4)	2 (0.7)	50 (5)	<0.0001
Sought medical advice for possible COVID-19				
GP visit	413/1859 (22)	16/61 (26)	159/334 (48)	<0.0001
Hospital visit	34/1868 (2)	1/61 (2)	21/336 (6)	<0.0001
Hospitalization	10/1871 (0.5)	0/61 (0)	10/338 (3)	<0.0001

* ECDC definition, n=3,028, onset ≥1st March, 3 missing in Elisa-S negative group

Table 3. Factors associated with a positive ELISA-S (vs negative or indeterminate)

	Positive/Total	% (Exact 95%CI)	Weighted prevalence estimates (%)	Odds-Ratio*	95%CI	P-value
Regions						<0.0001
Ile-de-France	552/6,348	8.7 (8.0; 9.4)	10.0 (9.1 ; 10.9)	2.64	2.20 ; 3.17	<0.0001
Grand-Est	270/3,434	7.9 (7.0 ; 8.8)	9.0 (7.7 ; 10.2)	2.44	1.99 ; 2.98	<0.0001
Nouvelle Aquitaine	161/4,846	3.3 (2.8 ; 3.9)	3.1 (2.4 ; 3.7)	Reference		
Age group (years)						<0.0001
<40	245/2,262	10.8 (9.6 ; 12.2)	10.9 (9.2 ; 12.4)	2.06	1.68 ; 2.53	<0.0001
[40-50]	332/2,897	11.5 (10.3 ; 12.7)	12.9 (11.2 ; 14.5)	2.14	1.77 ; 2.59	<0.0001
[50-60]	176/3,019	5.8 (5.0 ; 6.7)	5.6 (4.3 ; 6.8)	Reference		
[60-70]	133/3,272	4.1 (3.4 ; 4.8)	5.2 (4.0 ; 6.4)	0.68	0.54 ; 0.86	<0.0001
>=70	97/3,175	3.1 (2.5 ; 3.7)	3.8 (2.9 ; 4.6)	0.50	0.38 ; 0.65	<0.0001
Gender						0.0012
Male	327/5,809	5.6 (5.1 ; 6.3)	7.2 (6.2 ; 8.2)	Reference		
Female	656/8,818	7.4 (6.9 ; 8.0)	8.6 (7.7 ; 9.4)	1.27	1.10 ; 1.46	
Living Area						0.0006
Rural	118/2,176	5.4 (4.5 ; 6.5)	7.1 (5.6 ; 8.5)	Reference		
<20,000 inhab.	129/1,863	6.9 (5.8 ; 8.2)	8.9 (7.1 ; 10.5)	1.23	0.95 ; 1.60	0.1124
20-000-100,000 inhab.	211/2,797	7.5 (6.6 ; 8.6)	8.0 (6.6 ; 9.3)	1.34	1.06 ; 1.70	0.0135
>100,000 inhab.	524/7,769	6.7 (6.2 ; 7.3)	8.0 (7.2 ; 8.8)	1.59	1.27 ; 1.99	<0.0001
Missing	23					
Household size and composition						
Nb adults (inc. participant)						<0.0001
1	176/2,851	6.2 (5.3 ; 7.1)	7.2 (5.8 ; 8.4)	Reference		
2	329/6,533	5.0 (4.5 ; 5.6)	6.6 (5.7 ; 7.3)	0.84	0.69 ; 1.01	0.0685
3+	478/5,244	9.1 (8.4 ; 9.9)	10.3 (9.1 ; 11.4)	1.55	1.29 ; 1.86	<0.0001
Nb children (<18yrs)						<0.0001
0	574/10,848	5.3 (4.9 ; 5.7)	6.7 (6.0 ; 7.4)	Reference		
1+	409/3,780	10.8 (9.9 ; 11.9)	11.8 (10.3 ; 13.2)	2.16	1.89 ; 2.48	
Nb rooms						0.0069

1-2	131/1,696	7.7 (6.5 ; 9.1)	9.5 (7.8 ; 11.0)	1.06	0.86 ; 1.29	0.6076
3-4	421/5,715	7.4 (6.7 ; 8.1)	8.5 (7.5 ; 9.4)	Reference		
5-6	323/5,366	6.0 (5.4 ; 6.7)	6.8 (5.8 ; 7.8)	0.81	0.70 ; 0.98	0.0063
7+	100/1,700	5.9 (4.8 ; 7.1)	7.2 (5.2 ; 9.0)	0.78	0.62 ; 0.98	0.0317
Missing	151					
Total household monthly income						<0.0001
<1000€	10/201	5.0 (2.4 ; 9.0)	5.4 (1.6 ; 8.4)	0.60	0.32 ; 1.15	0.1234
1000-1499	18/447	4.0 (2.4 ; 6.3)	4.8 (2.2 ; 7.0)	0.48	0.30 ; 0.77	0.0026
1500-1999	61/1000	6.1 (4.7 ; 7.8)	8.2 (5.8 ; 10.3)	0.76	0.57 ; 0.99	0.0411
2000-2999	138/2,500	5.5 (4.7 ; 6.5)	7.1 (5.6; 8.4)	0.67	0.55 ; 0.82	<0.0001
3000-3999	207/3,426	6.0 (5.3 ; 6.9)	7.5 (6.2 ; 8.7)	0.77	0.65 ; 0.92	0.0034
>4000	477/6,045	7.9 (7.2 ; 8.6)	9.5 (8.4 ; 10.5)	Reference		
Missing	1,009					
Educational level						<0.0001
<High-school degree	59/1,629	3.6 (2.8 ; 4.7)	5.0 (3.5 ; 6.3)	Reference		
High-school degree or undergraduate	349/6,032	5.8 (5.2 ; 6.4)	7.8 (6.9 ; 8.7)	1.69	1.27 ; 2.24	0.0003
Graduate degree or doctorate	464/5,646	8.2 (7.5 ; 9.0)	9.3 (8.3 ; 10.2)	2.43	1.84 ; 3.21	<0.0001
Missing	1,321					
Professional activity before lockdown						<0.0001
Student	5/81	6.2 (2.0 ; 13.8)	7.2 (0.1 ; 12.6)	0.68	0.27 ; 1.68	0.4023
Working	741/8,309	8.9 (8.3 ; 9.6)	10.5 (9.5 ; 11.4)	Reference		
Looking for a job	30/402	7.5 (5.1 ; 10.5)	7.8 (4.7 ; 10.4)	0.83	0.57 ; 1.21	0.3305
Retired	182/5,381	3.4 (2.9 ; 3.9)	4.3 (3.5 ; 5.0)	0.35	0.30 ; 0.42	<0.0001
Not working due to health conditions	7/125	5.6 (2.3 ; 11.2)	3.8 (0.5 ; 6.3)	0.58	0.27 ; 1.25	0.1621
No professional activity (housewife or husband)	16/306	5.2 (3.0 ; 8.4)	7.2 (2.3 ; 11.1)	0.53	0.32 ; 0.88	0.0144
Missing	24					
Essential job position						
Healthcare worker Y vs N	60/568	10.6 (8.2; 13.4)	11.6 (8.3; 14.4)	1.62	1.23 ; 2.13	0.0007
Other essential job Y vs N	122/1,425	8.6 (7.2 ; 10.1)	11.9 (9.4 ; 14.0)	1.29	1.06 ; 1.58	0.0114
Professional activity during lockdown						<0.0001
Not working	240/6,295	3.8 (3.4 ; 4.3)	4.9 (4.1; 5.6)	0.39	0.33 ; 0.46	<0.0001
Stopped working	127/1,457	8.7 (7.3 ; 10.3)	8.3 (6.4 ; 10.0)	0.91	0.74 ; 1.12	0.3717

Working from home, remote working	410/4,444	9.2 (8.4 ; 10.1)	11.6 (10.1 ; 13.0)	Reference		
Partially working from home	75/759	9.9 (7.9 ; 12.2)	12.6 (9.4 ; 15.1)	1.06	0.82 ; 1.38	0.6516
Working outside home	96/1,134	8.5 (6.9 ; 10.2)	11.1 (8.7 ; 13.2)	0.89	0.70 ; 1.12	0.3062
Other	12/242	5.0 (2.6 ; 8.5)	7.8 (1.0 ; 12.6)	0.57	0.32 ; 1.04	0.0650
Missing	297					
Smoking status before lockdown						<0.0001
Active smoker	98/1,750	5.6 (4.6 ; 6.8)	7.1 (5.4 ; 8.7)	0.74	0.59 ; 0.92	0.0079
Ex-smoker	353/5,973	5.9 (5.3 ; 6.5)	7.1 (6.1 ; 8.0)	0.73	0.63 ; 0.84	<0.0001
Non smoker	516/6,670	7.7 (7.1 ; 8.4)	8.9 (7.9 ; 9.9)	Reference		
Missing	235					
Alcohol use before lockdown (in g/dy)						0.0821
<5	426/5,803	7.3 (6.7 ; 8.0)	8.5 (7.6 ; 9.3)	Reference		
[5,10[	176/2,641	6.7 (5.7 ; 7.7)	8.0 (6.5 ; 9.3)	0.94	0.78 ; 1.13	0.4971
[10,20[	205/2,963	6.9 (6.0; 7.9)	8.4 (6.9; 9.7)	1.03	0.86 ; 1.23	0.7380
[20,30[	63/1,359	4.6 (3.6 ; 5.9)	5.8 (3.6 ; 7.7)	0.70	0.53 ; 0.92	0.0201
≥30	64/1,128	5.7 (4.4 ; 7.2)	6.9 (4.5 ; 8.9)	0.87	0.66 ; 1.15	0.3276
Missing	734					
BMI (kg/m^2)						0.0390
<18.5	33/499	6.6 (4.6 ; 9.2)	5.6 (3.0; 7.7)	0.87	0.61 ; 1.25	0.4578
[18.5; 25[	619/8,521	7.3 (6.7 ; 7.8)	8.2 (7.5 ; 9.0)	Reference		
[25; 30[(overweight)	239/3,995	6.0 (5.3 ; 6.8)	8.2 (7.0 ; 9.3)	0.83	0.71 ; 0.97	0.0191
>=30 (obese)	82/1,409	5.8 (4.7 ; 7.2)	6.8 (5.0 ; 8.5)	0.78	0.61 ; 0.99	0.0400
Missing	204					
Chronic diseases						<0.0001
Yes	259/4,756	5.5 (4.8 ; 6.1)	6.7 (5.7; 7.7)	0.72	0.62 ; 0.83	<0.0001
No	715/9,767	7.3 (6.8 ; 7.9)	8.7 (7.8 ; 9.4)	Reference		
Don’t know	8/80	10.0 (4.4 ; 18.8)	9.9 (0.0 ; 16.2)	1.46	0.70 ; 3.06	0.3138
Missing	25					
Chronic diseases (Y vs N)						
Asthma, COPD, other respir. diseases	91/1,534	5.9 (4.8 ; 7.2)	6.5 (4.9 ; 7.9)	0.81	0.64 ; 1.02	0.0695
Diabetes	19/481	4.0 (2.4 ; 6.1)	5.8 (2.5 ; 8.5)	0.63	0.39 ; 1.00	0.0519
Hypertension	67/1,553	4.3 (3.4 ; 5.5)	4.9 (3.4 ; 6.3)	0.59	0.46 ; 0.77	<0.0001
Other cardiovascular diseases	19/451	4.2 (2.6 ; 6.5)	6.7 (3.3 ; 9.4)	0.64	0.40 ; 1.01	0.0569

Cancer	53/830	6.4 (4.8 ; 8.3)	7.6 (5.3 ; 9.7)	0.83	0.62 ; 1.11	0.1963
Anxiety, depression	30/404	7.4 (5.1 ; 10.4)	7.8 (3.8 ; 11.0)	1.08	0.74 ; 1.58	0.6955
Other	106/1,826	5.8 (4.8 ; 7.0)	7.3 (5.6 ; 8.8)	0.78	0.63 ; 0.97	0.0228
Missing	25					

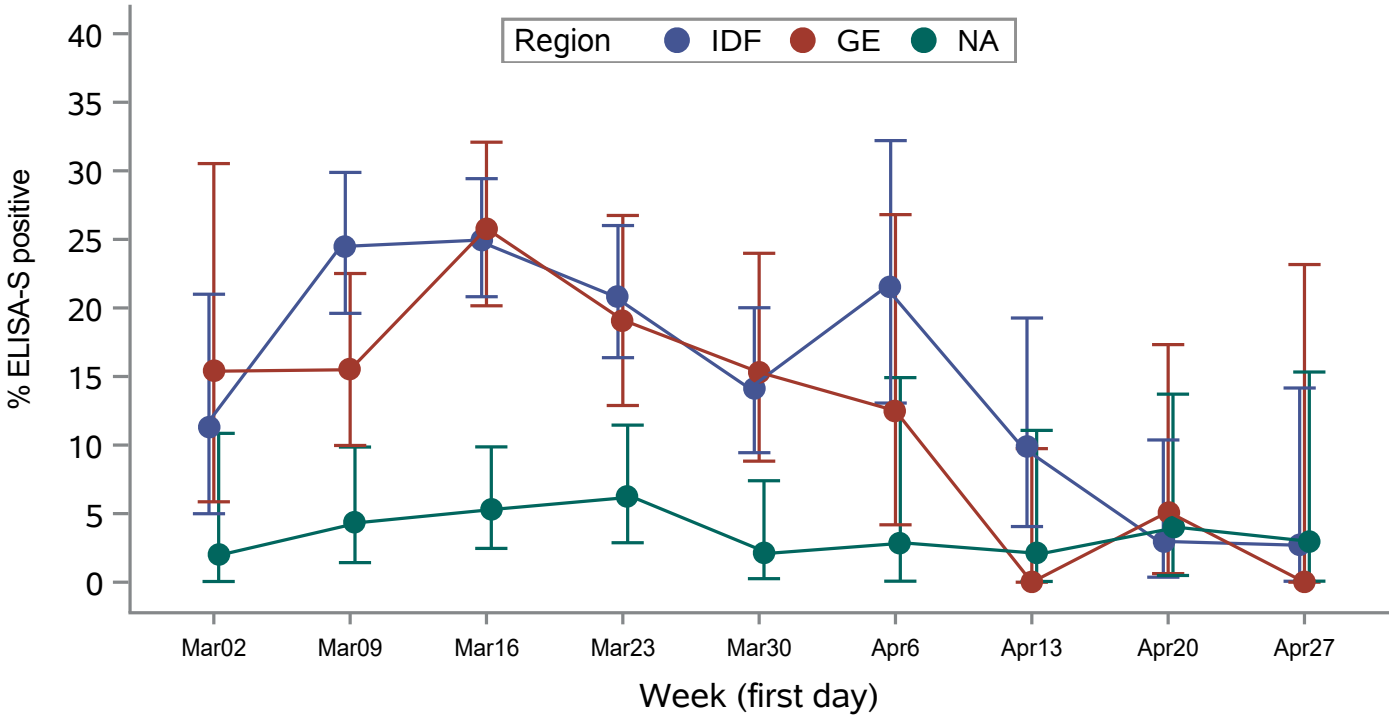
* with stratification on the source cohort.

Table 4. multivariable analysis of factors associated with a positive ELISA-S

	Odds-Ratio*	95%CI	P-value
Regions			
Ile-de-France	2.43	2.02 ; 2.93	<0.0001
Grand-Est	2.24	1.83 ; 2.75	<0.0001
Nouvelle Aquitaine	Reference		
Age group (years)			
<40	1.84	1.49 ; 2.28	<0.0001
[40-50[	1.92	1.57 ; 2.36	<0.0001
[50-60[	Reference		
[60-70[	0.77	0.60 ; 0.97	0.0299
>=70	0.56	0.42 ; 0.74	<0.0001
Gender			
Male	Reference		
Female	1.14	0.99 ; 1.32	0.0792
Household size and composition- Nb children (<18yrs)			
0	Reference		
1+	1.30	1.11 ; 1.53	0.0014
Smoking status before lockdown			
Active smoker	0.71	0.57 ; 0.89	0.0033
Ex-smoker	0.96	0.83 ; 1.11	0.5607
Non smoker	Reference		

235 participants – 16 with an ELISA-S positive result were excluded from the multivariable model due to missing smoking status

Figure 1.



Number of participants with possible COVID-19 by week of symptoms onset

IDF	71	286	409	292	184	79	71	67	37
GE	39	142	221	136	98	40	36	39	14
NA	49	115	169	145	95	35	48	50	34

Number of participants with ELISA-S positive test

IDF	8	70	102	61	26	17	7	2	1
GE	6	22	57	26	15	5	0	2	0
NA	1	5	9	9	2	1	1	2	1

Figure 2.

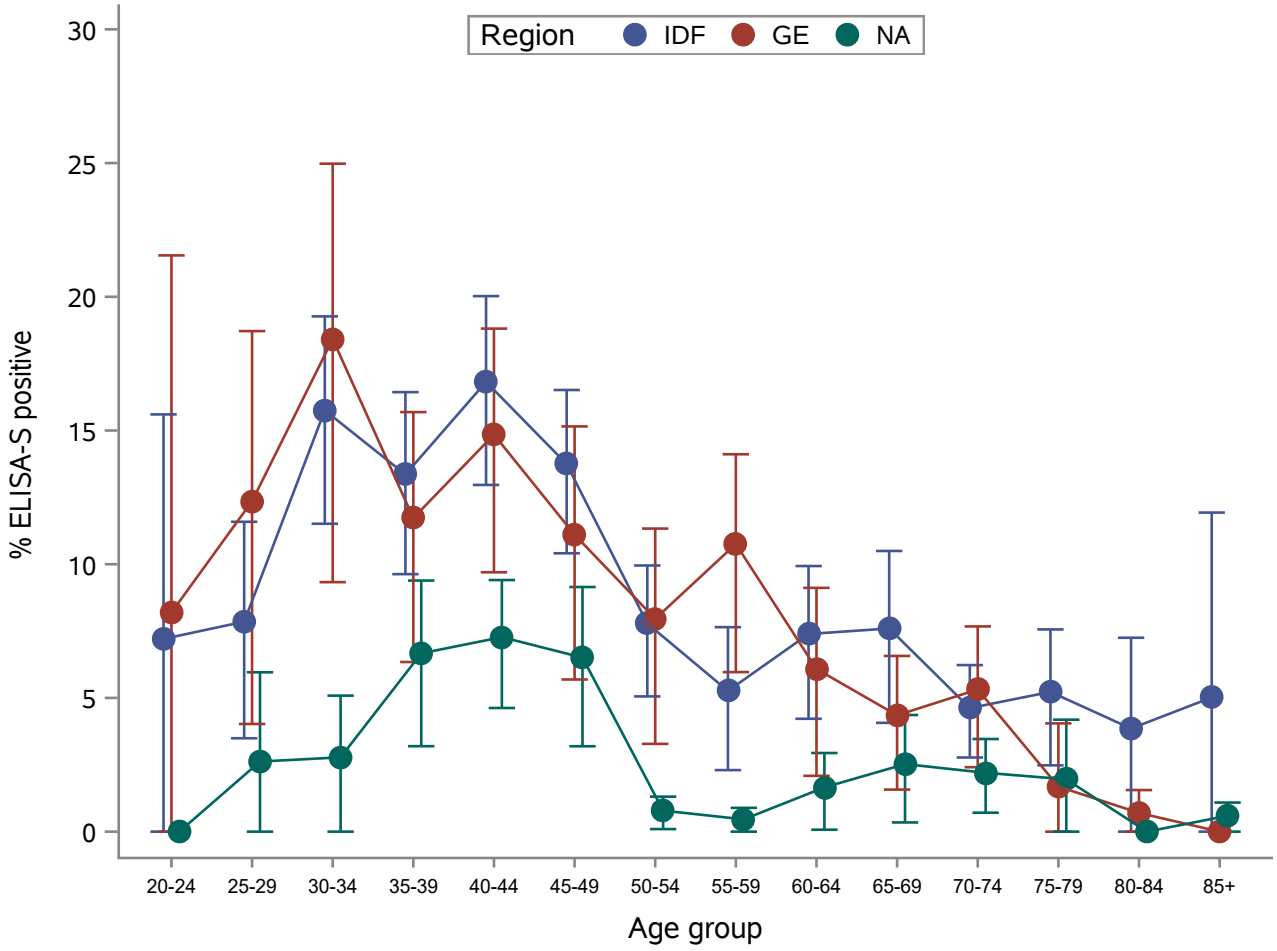
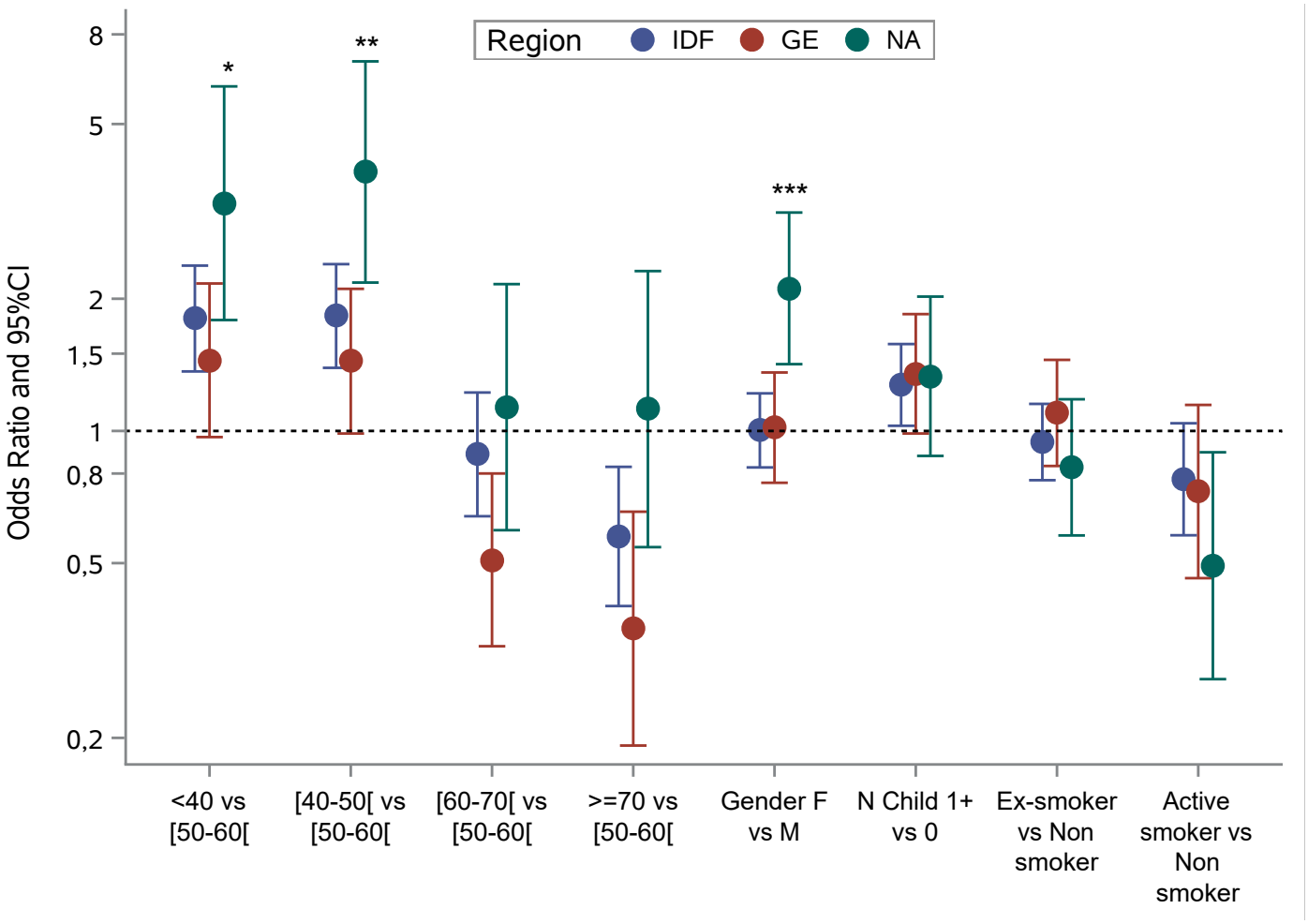


Figure 3.



* P=0.0284 ** P=0.0035 *** P=0.0006 (test for interaction in logistic model)