COVID-19 Susceptibility and Severity Risks in a Survey of Over 500,000 People

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Abstract

The growing toll of the COVID-19 pandemic has heightened the urgency of identifying individuals most at risk of infection and severe outcomes, underscoring the need to assess susceptibility and severity patterns in large datasets.[1] The AncestryDNA COVID-19 Study collected self-reported survey data on symptoms, outcomes, risk factors, and exposures for over 563,000 adult individuals in the U.S., including over 4,700 COVID-19 cases as measured by a self-reported positive nasal swab test. We observed significant associations between several risk factors and COVID-19 susceptibility and severity outcomes. Many of the susceptibility associations were accounted for by differences in known exposures; a notable exception was elevated susceptibility odds for males after adjusting for known exposures and age. We also leveraged the dataset to build risk models to robustly predict individualized COVID-19 susceptibility (area under the curve [AUC]=0.84) and severity outcomes including hospitalization and life-threatening critical illness amongst COVID-19 cases (AUC=0.87 and 0.90, respectively). The results highlight the value of self-reported epidemiological data at scale to provide public health insights into the evolving COVID-19 pandemic.

Main

The COVID-19 pandemic has resulted in nearly 35 million COVID-19 cases and more than 1,000,000 deaths worldwide,[2] including nearly 7.5 million cases and more than 210,000 deaths in the United States as of early October 2020.[3] The growing impact of the pandemic intensifies the need for enhanced understanding of COVID-19 susceptibility and severity risk factors, not only for public health experts, but also for individuals seeking to assess their own personalized risk. Prior research has hypothesized that differences in COVID-19 *susceptibility* are related to age,[4] sex-dependent immune responses,[5] and genetics,[6,7] while heightened *severity* of COVID-19 illness is associated with risk factors such as age,[1,4,8,9] sex,[5,10–12] underlying health conditions,[1,9,10,13,14] and genetic factors including the ABO blood group.[15] Self-reported survey data, which can easily be collected in the home, afford the opportunity to dynamically monitor the continually evolving pandemic and allow for real-time estimation of individual-level COVID-19 risk.[16–19] Furthermore, self-reported surveys allow for collection of information about known exposures, of which few epidemiological COVID-19 studies have explicitly accounted for in association analyses to date.[20]

In this paper, we aim to provide insight into factors associated with susceptibility and severity of COVID-19 using a large survey cohort of 563,141 AncestryDNA customers who have consented to participate in the AncestryDNA COVID-19 Study (Supplementary Tables 1-6).[6] We found that known exposure differences account for many associations for a positive COVID-19 test result.[18,21] Further analysis yielded evidence that males may be more susceptible to COVID-19 than females after adjusting for known exposures and age. While several previous reports have documented increased severity risk in males,[5,11,13] the finding of sex-based differences in

susceptibility here warrants further investigation. This study also replicates previous reports of strong associations between certain health conditions, age, and COVID-19 severity,[1,8–14] many of which remain significant after adjusting for other risk factors. We additionally investigated the symptomotology of COVID-19, and found that the symptoms most strongly associated with a positive test result are distinct from the symptoms most strongly associated with severity.[17,18,22,23]

Finally, we built predictive risk models for COVID-19 susceptibility and severity outcomes. For susceptibility, we designed two models and additionally applied two literature-based models[18] to predict COVID-19 cases among respondents reporting a test result. We also designed models to predict two different COVID-19 severity outcomes based on minimal information about demographics, health conditions, and symptoms: hospitalization due to COVID-19 infection (referred to throughout as "hospitalization") and progression of an infection to a life-threatening critical case among those reporting a positive COVID-19 result (referred to throughout as "critical case"; Methods).[13] All of the susceptibility and severity models performed robustly when evaluated in a large internal holdout dataset, and could potentially serve as tools for understanding individualized COVID-19 susceptibility and severity risk.[1,16–19,24] Assessing model performance in different populations offers insight into how well a risk model may generalize to the broader population. We assessed all of the risk models across different age, sex and genetic ancestry cohorts, and we report reasonably high performance in all cohorts.

Survey description. Survey responses were collected from AncestryDNA customers (see Methods and Supplementary Table 3 for demographic information). The survey collected self-reported responses to questions about COVID-19 test results, 15 symptoms among those who tested positive or who tested negative and had flu-like symptoms, disease progression for

positive testers, age, height, weight, known exposures to biological relatives, household members, patients or any other contacts with COVID-19, and 11 underlying health conditions (Supplementary Tables 1 and 2). Data were collected between 22 April 2020 and 6 July 2020, and the survey completion rate was approximately 95%. In general, the COVID-19 positive test rate and self-reported clinical outcomes are consistent with those reported by the U.S. Centers for Disease Control and Prevention (CDC) over a similar period (Supplementary Note 1).[21]

Association Analyses

Susceptibility. We investigated associations between COVID-19 testers reporting a positive or negative result and risk factors within the dataset (Figure 1, Methods, Supplementary Tables 7-12). Unadjusted odds ratios (ORs) were calculated using simple logistic regression, and adjusted ORs (aORs) were calculated using multiple logistic regression including known exposures, age, and sex as risk factors. Unadjusted ORs provide insight into which individual variables are correlated with testing positive for COVID-19, while adjusted ORs provide insight into which of these associations are not completely explained due to differences in age, sex, and known exposures.[25]

Known COVID-19 exposures, either through a household case (OR=26.03; 95% confidence interval [CI]=(22.26, 30.43)), biological relative (OR=5.77; 95% CI=(4.99, 6.68)), or other source of "direct" exposure (OR=6.94; 95% CI=(6.02, 7.99)) were the strongest predictors of a positive COVID-19 test result (Figure 1, Supplementary Table 7). In general, adjusting for known exposures, age, and sex resulted in attenuation of the ORs, with many associations becoming insignificant after adjustment (Figure 1, Supplementary Tables 8-9). Intriguingly, the OR for males was not attenuated after adjustment, and males remained at elevated odds after adjusting for known exposures and age (aOR=1.36; 95% CI=(1.19, 1.55); Figure 1, Supplementary Table 9). We also note that males and females reported comparable exposure burden, with males slightly more likely to report a household case of COVID-19 but less likely to report a case of COVID-19 among biological relatives (Supplementary Tables 11-12).

Younger individuals (ages 18-29; OR=1.51; 95% CI=(1.26, 1.81)), as well as individuals of admixed African-European (OR=1.48; 95% CI=(1.18, 1.85)) or admixed Amerindian ancestry (OR=1.49; 95% CI=(1.26, 1.77)) were significantly more likely to test positive compared to older individuals (ages 50-64, the largest age group in this cohort) or those of European ancestry, respectively (Supplementary Table 7). These individuals reported higher levels of COVID-19 cases within the household, cases among biological relatives, and/or other known "direct" COVID-19 exposures (Supplementary Tables 10-12).[26–30] Adjusting for age (ancestry groups only), sex, and known exposures attenuated the OR for all three of these groups (younger aOR=1.28; 95% CI=(1.03, 1.59), African-European aOR=1.23; 95% CI=(0.94, 1.62), and Amerindian aOR=1.27; 95% CI=(1.04, 1.57); Figure 1, Supplementary Table 9).

Individuals reporting pre-existing medical conditions (e.g., cancer, cardiovascular disease, chronic kidney disease [CKD], diabetes, hypertension) were less likely to test positive for COVID-19 (Figure 1, Supplementary Table 7). We observed significantly decreased odds of a known "direct" exposure to COVID-19, as well as significantly decreased odds of a household case of COVID-19, among such individuals relative to those without any health conditions (OR=0.71; 95% CI=(0.65, 0.78) and OR=0.74; 95% CI=(0.65, 0.84), respectively; Supplementary Tables 10-11). Notably, individuals with asthma and those with other lung conditions had significantly decreased odds of testing positive after adjusting for known exposures, age, and sex (OR=0.82; 95% CI=(0.69, 0.97) and OR=0.67; 95% CI=(0.44, 1.00), respectively; Supplementary Table 9).

Severity. We investigated associations between demographics, exposures, symptoms, and underlying health conditions for hospitalization and critical illness progression among COVID-19 cases (Figure 2, Supplementary Figure 1). Consistent with previous reports,[1,9,12–14] we observed positive associations between certain health conditions and COVID-19 severity outcomes; many of these associations remained significant after adjustment for age, sex, and obesity (BMI >= 30) (Figure 2, Supplementary Tables 13-16). COVID-19 cases reporting at least one underlying health condition were significantly more likely to progress to a critical case (OR=2.85; 95% CI=(1.78, 4.57); Figure 2, Supplementary Figure 1, Supplementary Table 15). Specific underlying health conditions that were associated with hospitalization and/or critical case progression included CKD, chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disease, and hypertension (Figure 2, Supplementary Figure 1, Supplementary Tables 13 and 15). Among individuals testing positive for COVID-19, the oldest (≥65 years) were significantly more likely to be hospitalized compared to those aged 50-64 (OR=1.70; 95% CI=(1.13, 2.56); Figure 2, Supplementary Table 13). Individuals of admixed African-European ancestry who tested positive were significantly more likely to report progression to a critical case, compared to those with European ancestry (OR=2.07; 95% CI=(1.03, 4.17); Supplementary Figure 1, Supplementary Table 15). Among COVID-19 cases, males were significantly more likely than females to report progression to a critical case (OR=1.54, 95%; CI=(1.00, 2.37); Supplementary Figure 1, Supplementary Table 15); these findings are consistent with CDC reports of increased ICU admittance rates in males (3% vs. 2%).[21]

Differential symptomology. Among symptomatic people who were reported a COVID-19 test result, those reporting moderate to severe change in taste or smell (OR=7.26; 95% CI=(5.54, 9.50)), fever (OR=1.60; 95% CI=(1.28, 2.01)), or feeling tired or fatigue (OR=1.41; 95% CI=(1.05, 1.89)) were more likely to test positive (Figure 3, Supplementary Table 7). Those reporting moderate to severe runny nose (OR=0.59; 95% CI=(0.47, 0.75)) or sore throat (OR=0.49; 95% CI=(0.39, 0.62)) were more likely to test negative, consistent with previous reports that these symptoms are more indicative of influenza or the common cold (Figure 3, Supplementary Table 7).[17,18,22] Change in taste or smell, a hallmark symptom of COVID-19 infection, was not associated with hospitalization (OR=0.77, 95% CI=(0.55, 1.07); Figure 3, Supplementary Table 13). By contrast, dyspnea (shortness of breath) was the most predictive of hospitalization and critical case progression (OR=7.52; 95% CI=(4.92, 11.49) and OR=11.55; 95% CI=(5.91, 22.59), respectively),[23] but was not associated with a positive test result (OR=1.14; 95% CI=(0.91, 1.44); Figure 3, Supplementary Tables 7, 13, and 15).

Predictive risk models. We developed models that predict an individual's COVID-19 risk (positive test result or severity). Many predictive models for COVID-19 infection and severity outcomes have been reported in the literature.[1,16–18,24,31] To date, few large-scale studies have investigated both susceptibility and severity risk within the same dataset, offering a consistent and comprehensive understanding of similarities and differences between the two outcomes.

For each of the risk models we developed, the survey data were divided into independent training and test cohorts, and additional association analyses were performed on the training data to guide the selection of risk factors for the models (Methods, Supplementary Tables 17-20). In contrast to association analyses, these risk models are based on penalized logistic regression with cross-validation in order to allow for transferability to independent cohorts.

The susceptibility models were designed to predict a COVID-19 result (positive or negative) from risk factors among testers. In addition to our own two models, we also replicated two self-reported models from the literature in order to assess how well our models perform relative to a respected benchmark.[18] In all, we compared four models: our model based on demographics and exposures (referred to throughout as "Dem + Exp"); our model based on demographics, exposures, and symptoms (referred to throughout as "Dem + Exp + Symp"); and the two literature-based models designed with nearly identical risk factors as reported previously in another large, self-reported study ("How We Feel" (HWF); models referred to as "HWF Exp + Symp" and "HWF Symp" throughout; Supplementary Note 2, Supplementary Table 20).[18]

All four susceptibility models performed robustly, with the Dem + Exp + Symp model achieving the highest overall performance (Figure 4, Supplementary Tables 21-24). The three models that

included one or more symptoms outperformed the model without symptoms (Dem + Exp), underscoring the value of self-reported symptoms for discriminating between cases and controls. The Dem + Exp model had an area under the curve (AUC) of 0.84 +/- 0.02, and the most predictive risk factor was having a household case of COVID-19. The Dem + Exp + Symp model had an AUC of 0.94 +/- 0.02, and the most predictive symptom was change in taste or smell. The HWF Exp + Symp model had an AUC of 0.90 +/- 0.03, and the HWF Symp model had an AUC of 0.87 +/- 0.03 (Supplementary Note 3). Each of the models performed comparably across different age, sex, and genetic ancestry cohorts (Figure 4, Supplementary Tables 21-24). We observed no significant overfitting in any of the models as evidenced by comparable train-test performances (Supplementary Table 25).

We also trained severity models to predict hospitalization and critical illness progression among COVID-19 cases. We included a number of risk factors and symptoms most associated with severe COVID-19 outcomes from the literature and/or our training dataset (Figure 3, Supplementary Tables 18 and 19); these included age,[1,8,9,13] sex,[1,5,11–13] morbid obesity (BMI >= 40),[1,32] and health conditions,[1,9,12–14] as well as shortness of breath,[23] fever, feeling tired or fatigue, dry cough, and diarrhea for symptoms. Both models performed robustly on an independent holdout dataset (Figure 4). The hospitalization model had an AUC of 0.87 +/- 0.03, and the critical case model had an AUC of 0.90 +/- 0.03. For both severity models, shortness of breath was the most predictive risk factor. We were concerned that this might seem obvious, so we designed models excluding this symptom which also achieved moderately high discriminative performance (AUC > 0.80; Supplementary Figure 5). The severity models performed comparably when stratifying by age, sex, and genetic ancestry (Figure 4,

Supplementary Tables 26-27), and there was no significant overfitting bias as evidenced by comparable train-test performances (Supplementary Table 25).

In contrast with susceptibility models, we did not evaluate the severity models against literature-based models, as the vast majority of these models include clinical factors (e.g., bloodwork) not measured in this self-reported dataset.[1,16,31] However, the models presented here perform on par with many previously reported models despite the absence of clinical factors, suggesting the potential value of self-reported data to identify the most at-risk COVID-19 individuals.[16,31]

Discussion. The AncestryDNA COVID-19 Study provides a highly complete, self-reported dataset that contains information about a plethora of risk factors in the context of COVID-19 susceptibility and severity outcomes. The self-report framework provides fast, low-cost, population-scale data that are particularly valuable in a pandemic, where knowledge is both limited and evolving rapidly based on changing circumstances. Additionally, the broad collection mechanism enables data-gathering from many more and potentially more diverse participants than typically seen in a medical setting, and participants can safely provide data from their homes. Moreover, self-reported data have been shown to be useful for estimating population prevalence,[19] and models built from these data may help to contextualize individual risk prior to infection with COVID-19.[1,16–18,24,31]

The study highlights exposure burden as the primary risk factor for COVID-19 susceptibility, and the importance of accounting for known exposures when assessing differences in susceptibility to COVID-19. Few studies have measured and explicitly adjusted for known

COVID-19 exposures at this scale.[20] We found elevated exposure levels for younger individuals, as well as individuals of admixed African-European or admixed Amerindian ancestry, which account for at least some of the elevated susceptibility risk for these individuals as evidenced by attenuation of ORs after adjustment for known exposures and age. This finding is consistent with previous reports about elevated exposure levels for younger and minority groups within the U.S.[26–30] By contrast, we found reduced exposure levels among those reporting one or more pre-existing health conditions. The lower exposure burden observed for these individuals may reflect pre-pandemic differences in public interactions or increased precautions to mitigate exposure, given published severity risks associated with these conditions.[1,9,13,14,33,34]

Importantly, we found elevated susceptibility risk in males after adjusting for age and known exposures, and the adjusted odds were not attenuated compared to the unadjusted odds. This finding is distinct from previous findings on elevated severity risk in males.[1,5,11] This result could be due to differences between men and women in behaviors, unknown exposures, biology, genetics,[5–7] or other risk factors not measured within this dataset.

Another major contribution of this study is the development of novel risk models for predicting an individual's COVID-19 susceptibility and severity risk. The risk models presented here perform comparably or better than similar and more complex models reported previously.[16–18,24,31] Although some previously reported risk models have been assessed in different age or sex cohorts,[16,17] we are not aware of any that have been assessed across genetic ancestry cohorts,[1,16–18,24,31] highlighting the potential utility and generalizability of these models to the broader population. Such models may be useful to clinicians to estimate an individual's risk of infection

and/or severity risk, or as a potential tool to triage testing given limited resources.[17,18,22] Just as importantly, the models could also be used by public health experts to understand population-level risk at large, given minimal self-reported risk factor data.

The COVID-19 pandemic has exacted a historic toll on healthcare systems and global economies, and continues to evolve based on changes in human behavior, public health guidelines, and societal factors. The large AncestryDNA network, well-established data collection mechanisms, and willingness of AncestryDNA customers to participate in COVID-19 research have rapidly come together in this study to elucidate more details about susceptibility and severe disease risk factors and help point the way to minimizing disease burden.

Methods

Ethics statement. Ethics statement. All data for this research project were from subjects who have provided informed consent to participate in AncestryDNA's Human Diversity Project, as reviewed and approved by our external institutional review board, Advarra (formerly Quorum). All data were de-identified prior to use.

Study population. Collection of self-reported COVID-19 outcomes from AncestryDNA customers who consented to research, participation criteria for the study, and the survey design are described in a genome-wide association study (GWAS) on a very similar AncestryDNA dataset, which identified three novel, genome-wide significant loci.[6] Here, participants reporting a negative test result were also assessed for symptoms and clinical outcomes. Analyses presented here were performed with data collected between 22 April and 6 July 2020.

Outcome definitions. The study assessed three outcomes: one for susceptibility and two for severity of COVID-19 infection. Cases for COVID-19 susceptibility were individuals who responded, “Yes, and was positive” to the question, “Have you been swab tested for COVID-19, commonly referred to as coronavirus?” Responders who answered, “Yes, and was negative” were used as controls for the susceptibility analysis.

The hospitalization outcome was defined among COVID-19-positive cases if a participant responded "Yes" to a binary question about experiencing symptoms due to COVID-19 illness and "Yes" to the hospitalization question ("Were you hospitalized due to these symptoms?). Controls were defined by a response of “No” to the hospitalization question in addition to reporting a self-reported positive COVID-19 test result.[6]

Critical cases of COVID-19 were defined via a response of “Yes” to one or more questions about ICU admittance (“Were you hospitalized in the Intensive Care Unit [ICU] with a ventilator?” or “Were you hospitalized in the Intensive Care Unit [ICU] with oxygen?”) or, alternatively, self-reported septic shock, organ failure, or respiratory failure resulting from a COVID-19 infection (“Have you had any of the following complications due to your illness? Select all that apply.”).[13]

Controls were defined by a response of "No" across all of these questions in addition to self-reporting a positive COVID-19 test result.

Genetic sex and ancestry definitions. All individuals were genotyped, using previously described general genotyping and quality control procedures.[35] Both sex and genetic ancestry were defined for individuals based on their genotypes. Genetic ancestry was estimated using a proprietary algorithm to estimate continental admixture proportions.[36] Briefly, this algorithm uses a hidden Markov model to estimate unphased diploid ancestry across the genome by comparing haplotype structure to a reference panel.

Data preparation for analysis. Multiple-choice categorical questions were one-hot ("dummy") encoded as binary risk factors with *k-1* degrees of freedom, where *k* corresponds to the number of fields for a given question. In this framework, a value of 0 across all *k-1* fields corresponds to a response of "None" or "None of the above" for a given question.

We considered several risk factors and outcomes questions in our association analyses and risk modeling efforts, some of which are summarized in Supplementary Tables 1 and 2. Based on the dependency structure within our survey, not every question was surfaced to every participant included within our study. As such, we made the following inferences:

- Participants reporting "No" to a binary question about symptoms arising from COVID-19 infection ("Did you experience symptoms as a result of your condition?") were designated as negatives for dependent questions about individual symptoms ("Between the beginning of February 2020 and now, have you had any of the following

symptoms?"), hospitalization due to symptoms ("Were you hospitalized due to these symptoms?"), ICU admittance due to symptoms ("Were you hospitalized in the Intensive Care Unit [ICU] with a ventilator?" or "Were you hospitalized in the Intensive Care Unit ([ICU] with oxygen?"), and medications prescribed due to symptoms ("Did a doctor treat you with medication for your illness?")

- Participants reporting "No" to a binary question about hospitalization ("Were you hospitalized due to these symptoms?") were assigned to a hospital duration of 0 days and designated as negative for ICU admittance due to symptoms.
- Participants reporting "No" to a binary question about medications prescribed due to symptoms ("Did a doctor treat you with medication for your illness?") were designated as negative for individual medication fields from a dependent question ("What medication were you treated with?").

Responses to a question about individual symptoms ("Between the beginning of February 2020 and now, have you had any of the following symptoms?") were converted to a binary variable based on the following mapping: 0 = None, Very Mild, Mild; 1 = Moderate, Severe, Very Severe.

Association analysis. Analyses were performed either with the *statsmodels* package in Python3 or in base R with the *glm* function. For each susceptibility and severity outcome and risk factor of interest, a simple logistic regression (LR) model was fit using unpenalized maximum likelihood.[37] LR models were fit on the entire cohort, except for age, sex, genetic ancestry, and obesity, where the models were fit only on the appropriate reference population drawn from the entire cohort (Supplementary Tables 7-16). Multiple logistic regression was used to adjust the ORs for known COVID-19 exposures and potentially confounding risk factors. The adjusted model includes age, sex, and four known exposures for susceptibility outcomes (Y/N if any); and age, sex, obesity (binarized if BMI >= 30), and health conditions (binarized if any) for severity outcomes (Figures 1 and 2). Individual adjustment variables were omitted when analyzing associations for risk factors within equivalent categories (e.g., age was not included in adjusted models for age bin risk factors).

For each risk factor, 95% confidence intervals (CIs) for the log odds ratio were estimated under the normal approximation. The significance threshold was Bonferroni-corrected for the 42 different risk factors examined, leading to an adjusted threshold of 0.05/42=0.0012.[37]

Risk model training and evaluation

Data splitting. All data were used in the OR analyses; data splitting was performed for risk modeling only. Prior to model training, the data were split with a fixed random seed. For susceptibility models without symptoms, 75% of the data were used for model training and 25% of the data were used for holdout evaluation. For severity models and susceptibility models with symptoms, 50% of the data were used for model training and 50% of the data were used for holdout evaluation. The larger holdout set allows for more robust stratified analyses of model performances, given the smaller overall cohort sizes for models with symptoms.

Predictive risk models. Logistic regression models were trained and evaluated using the *scikit-learn* package in Python. Here, we used lasso-penalized multiple logistic regression with cross-validation on the training dataset in order to select an optimal hyperparameterization for generalizability to independent test sets.[37] The penalized objective function for regression was weighted by inverse prevalence to address class imbalance and was framed as follows:

$$Cost(\boldsymbol{\beta}) = -\frac{1}{m}\sum_{j=1}^{m}\left(\frac{m}{m_{y=yj}}\right) y_j Ln\left(Logistic(\boldsymbol{\beta}\cdot\boldsymbol{x_j})\right) + \left(\frac{m}{m_{y=yj}}\right)(1-y_j)Ln\left(1-Logistic(\boldsymbol{\beta}\cdot\boldsymbol{x_j})\right) + \frac{\lambda}{m}\sum_{i=0}^{n}|\beta_i|$$

where m is the number of training examples, y_j is the true value of the outcome variable for the *jth* observation within the training data, $m_{y=yj}$ is the number of training examples with $y=y_j$, $\boldsymbol{\beta}$ corresponds to the vector of estimated coefficients for the risk factors, $\boldsymbol{x_j}$ is the vector of risk factor values for the *jth* observation within the training data, *Logistic* is the logistic (sigmoid) function, λ is the regularization parameter which favors simpler models via shrinkage of the beta

coefficients, *n* is the total number of risk factors in the model, β_i is the regression coefficient for the *ith* risk factor in the model, and *Ln* is the natural logarithm.

Risk factor selection and model training. We chose risk factors based on a minimal subset of nominally significant ORs within our training data as well as literature guidance.[1,4,5,9,11–14] For the susceptibility models without symptoms, we included a subset of exposure-related questions, based on the training OR analyses, as well as two demographic variables (age and sex). For susceptibility models with symptoms, we additionally included the five symptoms most differentiated between symptomatic negative and positive testers from our training ORs. For the severity models, we included pre-existing conditions, based on the training OR analyses, predictive symptoms within our training dataset[36], morbid obesity (BMI >= 40), age, and sex. The full list of risk factors for each model is included in Supplementary Table 20.

Once final risk factors were selected, we performed 5-fold cross-validation with grid search on our training dataset to select an optimal lasso regularization parameter lambda.[37] For the grid search, we scanned 8 different values for lambda, equally partitioned geometrically across a 4-log space. We then re-trained on the entire training dataset with the optimal lambda, and evaluated the final model on the holdout dataset.

Model thresholding. Phenotypes were predicted from the output of trained models based on a 50% probability threshold (i.e., logistic model output > 0.5). Sensitivity and specificity were then calculated based on the true vs. predicted binary outcomes.

392 **Estimation of performance error.** To estimate the error in our model performances, we
393 bootstrapped our holdout dataset 1,000 times to generate a sampling distribution for each
394 evaluation metric. We estimated the mean and 95% CIs for each metric based on the mean and
395 standard deviation of this sampling distribution.[37]
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397 # Figures, Tables, and Legends

398 ## Figures
399

400 **Figure 1:** Odds ratio visualization for susceptibility

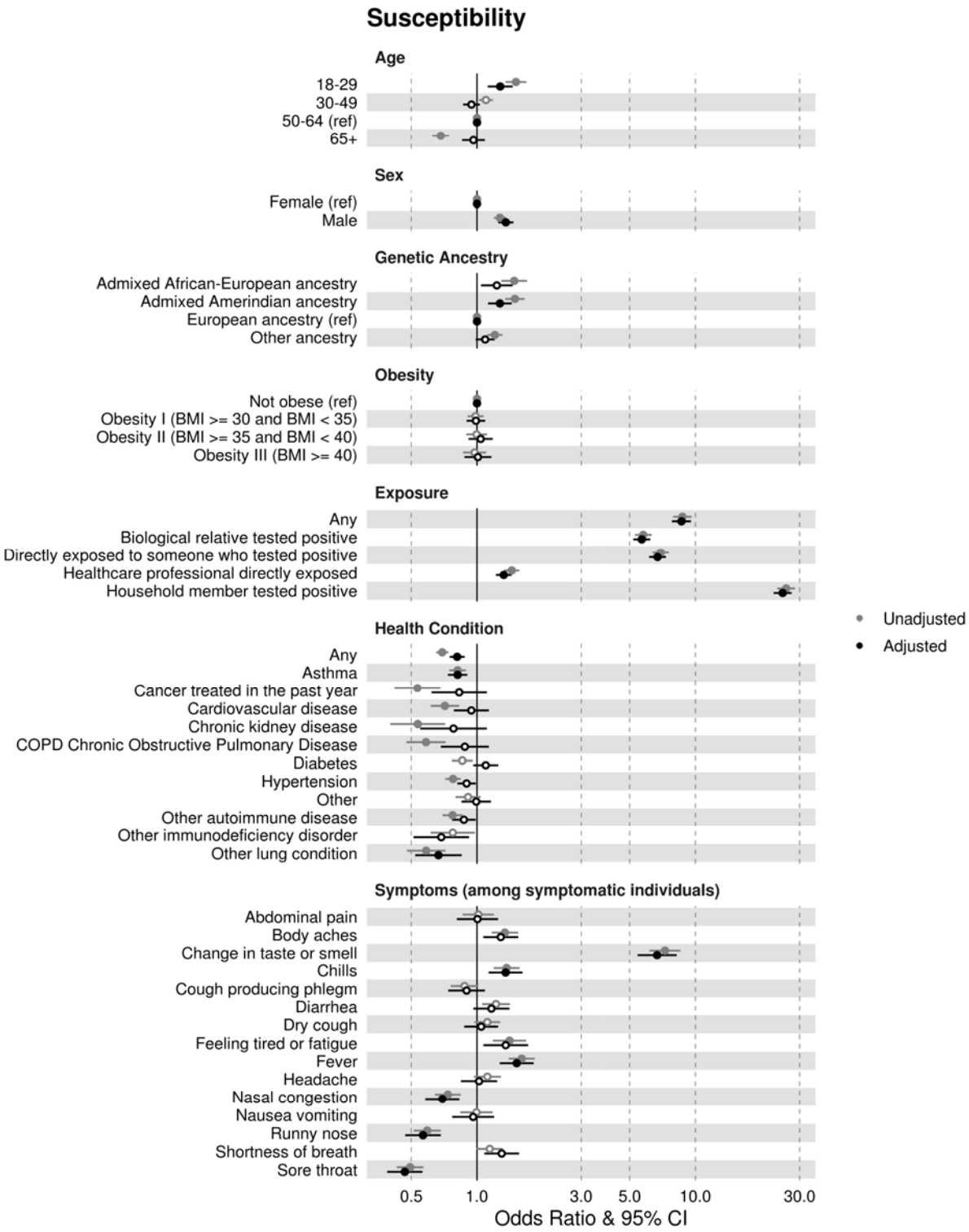

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Figure 1. Susceptibility odds ratios (ORs) and 95% confidence intervals (CIs) estimated from simple ("Unadjusted models," grey) and multiple ("Adjusted models," black) logistic regression with adjustment for other risk factors. Open circles indicate not significant (p-value > 0.05) after accounting for multiple hypothesis tests using Bonferroni correction. Age, sex, genetic ancestry, and obesity ORs were estimated in relation to the reference variables indicated. Exposure, health, and symptom ORs were each estimated separately as binary variables. Symptom ORs were estimated as binary variables among symptomatic testers only (Methods). Risk factor adjustments for susceptibility include: sex, age, and at least one known COVID-19 exposure (Methods). Where applicable, individual adjustment variables were omitted to avoid duplicate adjustment (Methods).

415 **Figure 2:** Odds ratio visualization for severity

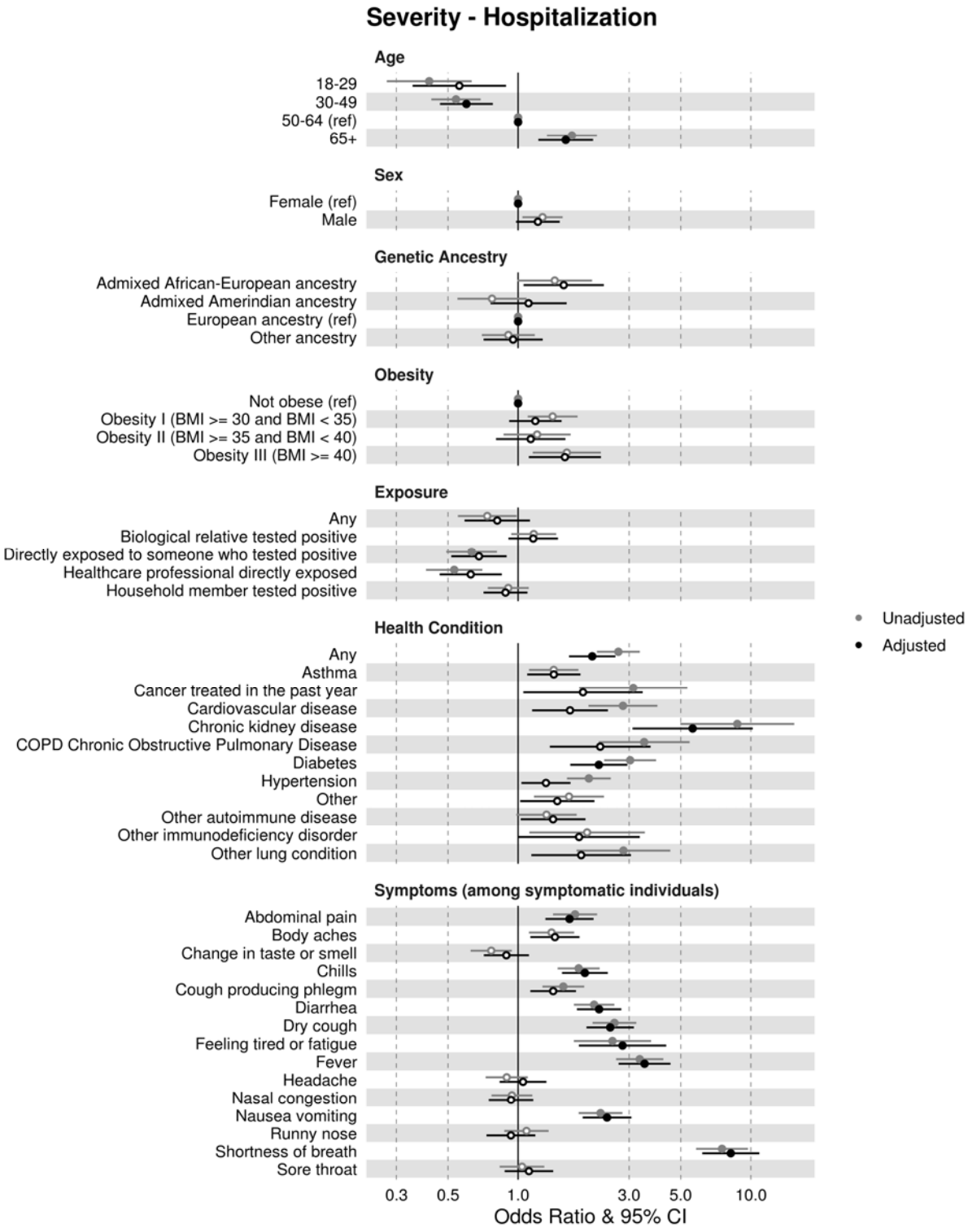

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Figure 2. Severity (hospitalization) odds ratios (ORs) and 95% confidence intervals (CIs) estimated from simple ("Unadjusted models," grey) and multiple ("Adjusted models," black) logistic regression with adjustment for other risk factors. Open circles indicate not significant (p-value > 0.05) after accounting for multiple hypothesis tests using Bonferroni correction. Age, sex, genetic ancestry, and obesity ORs were estimated in relation to the reference variables indicated. Exposure, health, and symptom ORs were each estimated separately as binary variables. Symptom ORs were estimated as binary variables among symptomatic testers only (Methods). Risk factor adjustments for severity include: sex, age, obesity (Y/N), and underlying health conditions (Y/N if any). Where applicable, individual adjustment variables were omitted to avoid duplicate adjustment (Methods). See Supplementary Figure 1 for critical case severity ORs.

Figure 3: Comparison of susceptibility and severity adjusted ORs

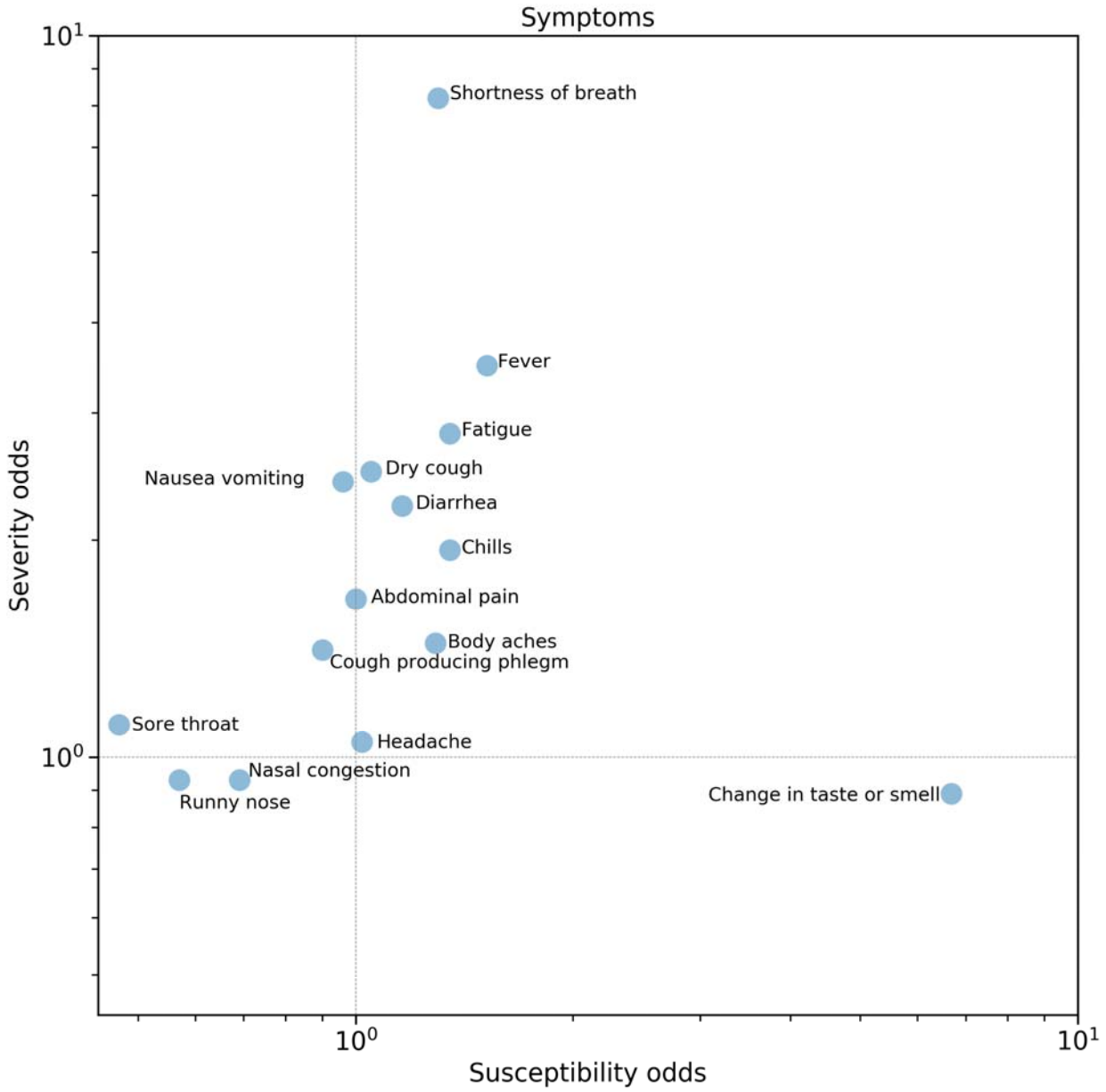

Figure 3. Comparison of susceptibility adjusted ORs (horizontal axis) and severity adjusted ORs (vertical axis) for symptoms in Figures 1 and 2. Severity aORs are for hospitalization. Note that aORs for susceptibility and severity are adjusted differently according to descriptions in Figure 1 and 2 captions. Adjusted ORs are plotted on a log scale for visibility. Shortness of breath is the strongest indicator of increased severity, while change in taste or smell is the

strongest indicator for testing positive for COVID-19 among symptomatic individuals (Methods). See Supplementary Figure 2 for demographic, health condition, and exposure aORs.

442 **Figure 4:** Risk model performance

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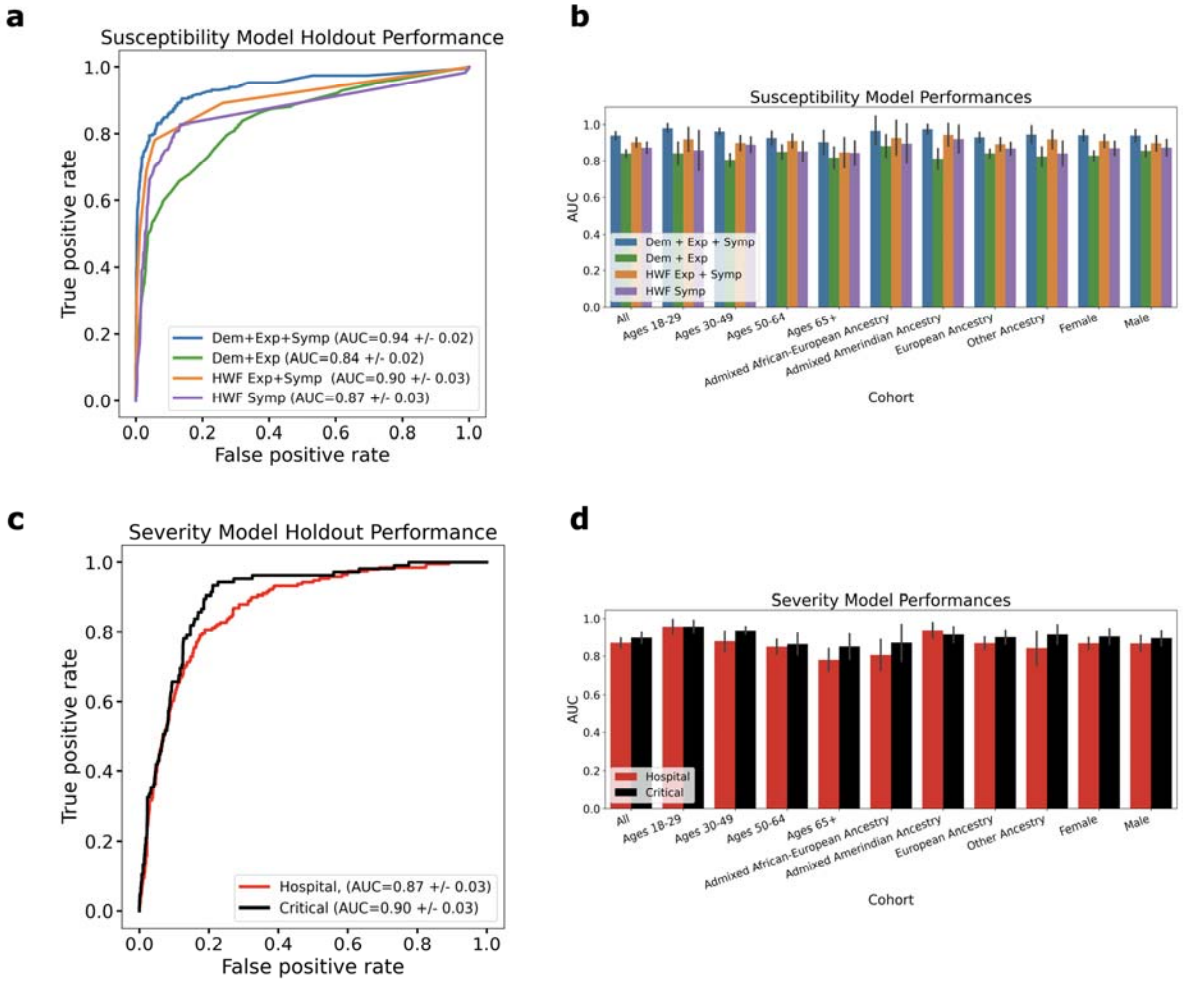

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445 **Figure 4. Performance of risk models on independent holdout data.** a) Receiver operating
446 characteristic (ROC) curves for susceptibility models to predict COVID-19 cases among testers
447 reporting a result (positive or negative). b) Area under the curve (AUC) for the four
448 susceptibility models in (a), stratified by cohort. “All” represents everyone in (a). c) ROC curves
449 for severity models to predict either hospitalization (red) or critical illness progression (black)

among COVID-19 cases. d) Area under the curve (AUC) for the two severity models in (b), stratified by cohort. “All” represents everyone in (c). Refer to Methods as well as Supplementary Figure 3 and Supplementary Tables 20-27 for additional model performance data and model risk factor information.

Data availability We plan to make a dataset available to qualified scientists through the European Genome-phenome Archive (EGA). The EGA dataset includes the risk factors and outcomes studied here, for a different set of individuals.

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Author contributions SCK and SRM contributed equally to the manuscript and wrote the first draft of the paper. ARG provided direct project guidance and lead the COVID-19 research teams. SCK, SRM, BR performed the association analyses. SCK developed and assessed the risk models. MVC and KAR designed the COVID-19 survey questionnaire. SCK and DP supported the dataset creation. GHLR supported the phenotype definitions. MVC and NDB built the demographic tables. SCK, SRM, BR, MVC, GHLR, ARG, and KAR helped with additional analyses and interpretation. MZ, DP, DT, KD, MP, HG, AKHB helped with the EGA dataset. The AncestryDNA Science Team contributed to additional work, allowing for the completion of the COVID-19 research and manuscript. KAR, ELH, and CAB provided additional project guidance. All authors contributed to the final manuscript.

Competing interests The authors declare competing financial interests: authors affiliated with AncestryDNA may have equity in Ancestry.

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Supplementary Materials

Supplementary Notes

Supplementary Note 1. Comparison of AncestryDNA Data to CDC Data. In general, the COVID-19 testing results are consistent with those reported by the U.S. Centers for Disease Control and Prevention (CDC) over a similar period.[21] For example, the CDC reported a 12% cumulative overall positive test rate from 1 March to 30 May 2020, while 14.1% of AncestryDNA survey participants reported testing positive (the denominator includes tests with "results pending"). For hospitalization, the CDC reported that 14% of individuals testing positive for COVID-19 were hospitalized, and 2% were admitted to an intensive care unit (ICU), between 22 January and 30 May 2020. Among the AncestryDNA survey respondents, 11% of those reporting a positive COVID-19 test were hospitalized, and 4.9% were admitted to ICU between 22 April and 6 July 2020.

Supplementary Note 2. Risk factors for predictive susceptibility models. The HWF Exp + Symp model includes three risk factors, including two exposures and one symptom (change in taste or smell, Supplementary Table 20). The HWF Symp model includes seven symptoms most commonly associated with COVID-19 according to the CDC (Supplementary Table 20).[18,38] For the Dem + Exp and Dem + Exp + Symp models, we incorporated responses to several exposure questions that were primary risk factors in the OR analysis of the training set (Methods and Supplementary Table 20).[18,39,40] We also considered age and sex, given their nominal association with COVID-19 in our ORs in the training dataset, as well as reports about these variables as

risk factors (Supplementary Table 17).[4,5,30] For Dem + Exp + Symp model, we selected the most differentiated symptoms between cases and controls amongst symptomatic COVID-19 testers within the training dataset (Supplementary Table 17), including fever, change in taste or smell, feeling tired/fatigued, runny nose, and sore throat.[17,18,22]

Supplementary Note 3. Comparison of Ancestry and HWF Cohorts and Performances. The HWF models performed better when trained and evaluated on the AncestryDNA dataset as compared with the HWF dataset, particularly for the symptoms-only model (HWF Symp: AncestryDNA-trained AUC=0.87 and HWF-trained AUC=0.76 and HWF Exp + Symp: AncestryDNA-trained AUC=0.90 and HWF-trained AUC=0.87; Figure 4).[18] This result could be due to differences in survey flow design, demographics, or the relative prevalences of self-reported symptoms between the two datasets. We re-trained and evaluated our models on a subset of symptomatic COVID-19 testers (positives and negatives) reporting at least one symptom of moderate or greater intensity. The performances of all models that included symptoms were slightly attenuated in this cohort, with AUCs for the HWF models approaching previous reports (HWF Symp: AncestryDNA-trained AUC=0.80 and HWF Exp + Symp: AncestryDNA-trained AUC=0.87); the model without symptoms performed the same (Supplementary Figure 4). This suggests that predicting COVID-19 cases on the basis of symptoms alone is more challenging when symptoms are less differentiated between positive and negative testers.

Supplementary Tables

Supplementary Table 1. Selected subset of survey questions considered in the context of COVID-19 severity outcomes analysis and modeling efforts.

Risk factor description	Question	Possible responses
COVID-19 test result	Have you been swab tested for COVID-19, commonly referred to as coronavirus?	Yes, and was positive; Yes, and was negative; Yes, and my results are pending; No, but I have had flu-like symptoms with a fever at some point since the beginning of February 2020; No, and I have not had flu-like symptoms at some point since the beginning of February 2020
Case amongst direct biological relatives (multi-choice)	Have any of your biological relatives tested positive for COVID-19? Select all that apply.	Grandparent(s); Parent(s); Child(ren); Sibling(s); Other; None
Healthcare worker routinely exposed to COVID-19	Are you a healthcare professional working directly with or in close physical proximity to patients who have tested positive for COVID-19?	Yes; No; Not sure
Household case of COVID-19	Has someone in your household tested positive for COVID-19?	Yes; No; Not sure
Number of household cases of COVID-19	How many people in your household have tested positive for COVID-19?	Numeric
Known direct COVID-19 exposure	Have you been directly exposed to someone who has tested positive for COVID-19?	Yes; No; Not sure
Health condition(s)	Do you currently have any of the following health conditions? Select all that apply.	Asthma,COPD (Chronic Obstructive Pulmonary Disease); Other lung condition; Cancer (treated in the past year); Cardiovascular disease; Chronic kidney disease; Diabetes; Hypertension; Organ failure requiring a transplant (in the last year); Blood disorder requiring hematopoietic stem cell / bone marrow transplant; Other autoimmune disease; Other immunodeficiency disorder; Other; None; Not sure

The survey flow was as described previously,[6] with the addition of symptom and clincial assessment for negative testers.

Supplementary Table 2. Selected risk factors considered in susceptibility or severity outcomes analysis and modeling efforts.

Risk factor description	Question	Possible responses
COVID-19 test result	Have you been swab tested for COVID-19, commonly referred to as coronavirus?	Yes, and was positive; Yes, and was negative; Yes, and my results are pending; No, but I have had flu-like symptoms with a fever at some point since the beginning of February 2020; No, and I have not had flu-like symptoms at some point since the beginning of February 2020
Symptoms (binary)	Did you experience symptoms as a result of your condition?	Yes; No; Not sure
Symptoms (multi-choice)	Between the beginning of February 2020 and now, have you had any of the following symptoms?	Fever; Shortness of breath; Dry cough; Nasal congestion; Runny nose; Sore throat; Feeling tired or fatigue; Chills; Body aches; Headache; Cough producing phlegm; Abdominal pain; Nausea or vomiting; Diarrhea; Change in taste or smell
Symptom duration (multi-choice)	How long did these symptoms last?	Less than 1 day; 1-3 days; 4-7 days; 8-14 days; 2 weeks to a month; 1-3 months; More than 3 months
Hospitalization	Were you hospitalized due to these symptoms?	Yes; No; Not sure
Hospital duration	How long were you hospitalized?	Numeric
ICU with ventilator	Were you hospitalized in the Intensive Care Unit (ICU) with a ventilator?	Yes; No; Not sure
ICU with oxygen	Were you hospitalized in the Intensive Care Unit (ICU) with oxygen?	Yes; No; Not sure
Illness complications (multi-choice)	Have you had any of the following complications due to your illness? Select all that apply.	None; Pneumonia; Severe pneumonia leading to hospitalization; Respiratory failure; Septic shock; Multiple organ dysfunction or failure; Blood clots; Stroke; Other

The survey flow was as described previously,[6] with the addition of symptom and clincial assessment for negative testers.

Supplementary Table 3. Study population demographic summary

	COVID-19 Nasopharyngeal Swab Test Positive	COVID-19 Nasopharyngeal Swab Test Negative	Full AncestryDNA COVID-19 Cohort
	n = 4,726	*n = 28,872*	*n = 563,141*
Age			
Median, mean (sd)	49, 49.49 (15.43)	53, 52.68 (15.5)	56, 53.90 (16.13)
Bins (Counts, %)			
18-30	600 (0.13)	2496 (0.09)	52580 (0.09)
31-40	941 (0.2)	5001 (0.17)	87261 (0.15)
41-50	926 (0.2)	5333 (0.18)	90473 (0.16)
51-60	1057 (0.22)	6009 (0.21)	108062 (0.19)
61-70	735 (0.16)	5961 (0.21)	128200 (0.23)
71-90	467 (0.10)	4072 (0.14)	96565 (0.17)
Genetic Sex (counts, %)			
Female	3013 (0.64)	19945 (0.69)	380349 (0.67)
Male	1706 (0.36)	8867 (0.31)	183153 (0.32)
Genetic Ancestry Continental Groupings			
Admixed African-European ancestry	275 (0.06)	1244 (0.04)	17019 (0.03)
Admixed Amerindian ancestry	520 (0.11)	2336 (0.08)	36865 (0.07)
European ancestry	3026 (0.64)	20269 (0.7)	424328 (0.75)
Other ancestry	905 (0.19)	5023 (0.17)	84929 (0.15)
Pre-existing health conditions (any)	1911 (0.46)	15261 (0.55)	255788 (0.47)
BMI (med, mean, sd)	28.59, 29.83 (7.04)	28.67, 29.92 (7.05)	28.29, 29.53 (6.87)
Underweight (count, %)	<100	204	4407
Healthy (count, %)	971	6442	139565
Overweight (count, %)	1225	8503	172941
Obese (count, %)	1629	11264	203325
Flu			
Shot (yes)	2656 (0.63)	19856 (0.71)	356144 (0.65)
Test Dx (yes)	198 (0.05)	1180 (0.04)	11726 (0.02)
Symptoms (tested pos.)			
General, yes (count, % of pos.)	3862 (0.87)		9237 (0.47)
Hospitalization (count, % of positives)	453 (0.11)		1397 (0.02)
Duration, days (med, mean, sd)	5, 7.62 (9.08)		3, 4.78 (7.22)

Supplementary Table 4. Demographics for susceptibility modeling cohort

	COVID-19 Nasopharyngeal Swab Test Positive	COVID-19 Nasopharyngeal Swab Test Negative	Total Susceptibility modeling cohort (symptom data not required)
	n = 2,505	*n* = 16,830	*n* = 19,335
Age			
Median, mean (sd)	48, 47.96 (14.68)	53, 52.93 (15.5)	53, 52.29 (15.49)
Bins (Counts, %)			
18-30	350 (0.14)	1404 (0.08)	1754 (0.09)
31-40	531 (0.21)	2882 (0.17)	3413 (0.18)
41-50	511 (0.2)	3073 (0.18)	3584 (0.19)
51-60	580 (0.23)	3478 (0.21)	4058 (0.21)
61-70	365 (0.15)	3548 (0.21)	3913 (0.20)
71-90	168 (0.07)	2445 (0.15)	2613 (0.14)
Genetic Sex (counts, %)			
Female	1646 (0.66)	11688 (0.69)	13334 (0.69)
Male	859 (0.34)	5142 (0.31)	6001 (0.31)
Genetic Ancestry Continental Groupings			
Admixed African-European ancestry	130 (0.05)	730 (0.04)	860 (0.04)
Admixed Amerindian ancestry	287 (0.11)	1319 (0.08)	1606 (0.08)
European ancestry	1633 (0.65)	11886 (0.71)	13519 (0.70)
Other ancestry	455 (0.18)	2885 (0.17)	3350 (0.17)
Pre-existing health conditions (any)	1131 (0.45)	9168 (0.54)	10299 (0.53)
BMI (med, mean, sd)			
Total	28.7, 29.95 (7.16)	28.52, 29.88 (6.99)	28.73, 30.02 (7.08)
Underweight (count, %)	<100	111	135
Healthy (count, %)	629	4051	4680
Overweight (count, %)	759	5433	6192
Obese (count, %)	1069	7012	8081
Flu			
Shot (yes)	1617 (0.65)	12029 (0.71)	13646 (0.71)
Test Dx (yes)	125 (0.05)	761 (0.05)	886 (0.05)
Symptoms (tested pos.)			
General, yes (count, % of pos.)	2254 (0.9)	-	2905 (0.45)
Hospitalization (count, % of positives)	260 (0.11)	-	292 (0.09)
Duration, days (med, mean, sd)	5, 6.68 (8.46)	-	4.5, 6.42 (8.08)

Supplementary Table 5. Demographics for severity modeling cohort

	COVID-19 Nasopharyngeal Swab Test Positive
	n = 3,585
Age	
Median, mean (sd)	49, 48.62 (14.68)
Bins (Counts, %)	
18-30	463 (0.13)
31-40	725 (0.2)
41-50	748 (0.21)
51-60	832 (0.23)
61-70	555 (0.15)
71-90	262 (0.07)
Genetic Sex (counts, %)	
Female	2303 (0.64)
Male	1282 (0.36)
Genetic Ancestry Continental Groupings	
Admixed African-European ancestry	203 (0.06)
Admixed Amerindian ancestry	397 (0.11)
European ancestry	2317 (0.65)
Other ancestry	668 (0.19)
Pre-existing health conditions (any)	1666 (0.46)
BMI (med, mean, sd)	28.67, 29.83 (7.03)
Underweight (count, %)	<100
Healthy (count, %)	884
Overweight (count, %)	1128
Obese (count, %)	1498
Flu	
Shot (yes)	2293 (0.64)
Test Dx (yes)	174 (0.05)
Symptoms (tested pos.)	
General, yes (count, % of pos.)	3236 (0.9)
Hospitalization (count, % of positives)	391 (0.11)
Duration, days (med, mean, sd)	5, 7.34 (8.73)

554 **Supplementary Table 6. Demographics for susceptibility models with symptoms**

	Susceptibility modeling cohort (with symptom data)
	n = 4,094
Age	
Median, mean (sd)	58, 55.7 (15.82)
Bins (Counts, %)	
18-30	293 (0.07)
31-40	567 (0.14)
41-50	641 (0.16)
51-60	795 (0.19)
61-70	982 (0.24)
71-90	816 (0.20)
Genetic Sex (counts, %)	
Female	2744 (0.67)
Male	1350 (0.33)
Genetic Ancestry Continental Groupings	
Admixed African-European ancestry	172 (0.04)
Admixed Amerindian ancestry	298 (0.07)
European ancestry	2927 (0.72)
Other ancestry	666 (0.16)
Pre-existing health conditions (any)	2205 (0.54)
BMI (med, mean, sd)	28.59, 29.8 (6.84)
Underweight (count, %)	<100
Healthy (count, %)	1007
Overweight (count, %)	1335
Obese (count, %)	1662
Flu	
Shot (yes)	2935 (0.72)
Test Dx (yes)	160 (0.04)
Symptoms (tested pos.)	
General, yes (count, % of pos.)	1037 (0.25)
Hospitalization (count, % of positives)	<100
Duration, days (med, mean, sd)	5, 7.53 (10.11)

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557 **Supplementary Table 7. Unadjusted risk factor odds ratios for COVID-19 susceptibility**

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RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.51	(1.26, 1.81)	0.4108	0.0563	3.05E-13	1.28E-11
Ages 30-49	1.10	(0.97, 1.24)	0.0944	0.0377	1.22E-02	5.14E-01
Ages 50-64	1.00		0		nan	nan
Ages 65+	0.68	(0.59, 0.79)	-0.3819	0.0454	0.00E+00	0.00E+00
GENETIC ANCESTRY						
Admixed African-European	1.48	(1.18, 1.85)	0.3925	0.0694	1.57E-08	6.58E-07
European	1.00		0		nan	nan
Admixed Amerindian	1.49	(1.26, 1.77)	0.3995	0.0523	2.10E-14	8.82E-13
Other	1.21	(1.06, 1.38)	0.188	0.041	4.62E-06	1.94E-04
EXPOSURE						
Any	8.72	(7.42, 10.26)	2.1659	0.0501	0.00E+00	0.00E+00
Biological relative tested positive	5.77	(4.99, 6.68)	1.7529	0.045	0.00E+00	0.00E+00
Directly exposed to someone who tested positive	6.94	(6.02, 7.99)	1.9366	0.0438	0.00E+00	0.00E+00
Healthcare worker directly exposed	1.44	(1.26, 1.65)	0.367	0.0408	2.31E-19	9.69E-18
Household member tested positive	26.03	(22.26, 30.43)	3.2591	0.0482	0.00E+00	0.00E+00
HEALTH CONDITIONS						
Asthma	0.81	(0.71, 0.94)	-0.2046	0.0446	4.55E-06	1.91E-04
COPD (Chronic Obstructive Pulmonary Disease)	0.58	(0.41, 0.82)	-0.5374	0.1057	3.72E-07	1.56E-05
Cancer treated in the past year	0.53	(0.36, 0.80)	-0.6283	0.1237	3.80E-07	1.59E-05
Cardiovascular disease	0.71	(0.56, 0.91)	-0.3383	0.0762	9.12E-06	3.83E-04
Chronic kidney disease	0.54	(0.33, 0.87)	-0.6241	0.148	2.48E-05	1.04E-03
Diabetes	0.86	(0.71, 1.03)	-0.1547	0.0561	5.79E-03	2.43E-01
Hypertension	0.78	(0.68, 0.89)	-0.2522	0.0411	8.08E-10	3.40E-08
Other	0.91	(0.73, 1.13)	-0.0939	0.0675	1.64E-01	1.00E+00
Other autoimmune disease	0.77	(0.65, 0.92)	-0.2571	0.054	1.95E-06	8.20E-05
Other immunodeficiency disorder	0.77	(0.53, 1.14)	-0.2552	0.1194	3.25E-02	1.00E+00
Other lung condition	0.59	(0.42, 0.82)	-0.5355	0.1037	2.45E-07	1.03E-05

Any	0.69	(0.62, 0.77)	-0.3667	0.0336	0.00E+00	0.00E+00
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	0.99	(0.86, 1.13)	-0.0146	0.043	7.35E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.00	(0.83, 1.19)	-0.0042	0.056	9.41E-01	1.00E+00
obesity III (BMI >= 40)	0.97	(0.80, 1.19)	-0.0255	0.0622	6.81E-01	1.00E+00
Not obese	1.00		0		nan	nan
GENETIC SEX						
Female	1.00		0		nan	nan
Male	1.27	(1.14, 1.42)	0.2419	0.0329	1.89E-13	7.95E-12
SYMPTOMS						
Abdominal pain	1.01	(0.77, 1.33)	0.0139	0.0841	8.69E-01	1.00E+00
Body aches	1.34	(1.06, 1.69)	0.2945	0.0717	4.04E-05	1.70E-03
Change in taste or smell	7.26	(5.54, 9.50)	1.9819	0.0832	1.62E-125	6.81E-124
Chills	1.37	(1.09, 1.71)	0.3126	0.0697	7.23E-06	3.04E-04
Cough producing phlegm	0.88	(0.69, 1.12)	-0.1318	0.0746	7.74E-02	1.00E+00
Diarrhea	1.22	(0.96, 1.56)	0.2006	0.0745	7.11E-03	2.99E-01
Dry cough	1.12	(0.89, 1.40)	0.109	0.0694	1.16E-01	1.00E+00
Feeling tired or fatigue	1.41	(1.05, 1.89)	0.343	0.0901	1.41E-04	5.91E-03
Fever	1.60	(1.28, 2.01)	0.4715	0.0701	1.74E-11	7.30E-10
Headache	1.12	(0.88, 1.41)	0.1098	0.0728	1.32E-01	1.00E+00
Nasal congestion	0.74	(0.59, 0.92)	-0.3072	0.0696	1.01E-05	4.24E-04
Nausea or vomiting	0.99	(0.75, 1.32)	-0.0055	0.0867	9.50E-01	1.00E+00
Runny nose	0.59	(0.47, 0.75)	-0.5245	0.0725	4.49E-13	1.89E-11
Shortness of breath	1.14	(0.91, 1.44)	0.1343	0.0705	5.67E-02	1.00E+00
Sore throat	0.49	(0.39, 0.62)	-0.7052	0.0717	8.10E-23	0.00E+00

Unadjusted odds ratios for a positive COVID-19 test were calculated among survey participants reporting a test result (positive or negative) based on the self-reported response to the following question: “Have you been swab tested for COVID-19, commonly referred to as coronavirus?” The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods).

Supplementary Table 8. Risk factors odds ratios for COVID-19 susceptibility, adjusted for exposure questions

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.27	(1.02, 1.57)	0.2364	0.0670	4.22E-04	1.77E-02
Ages 30-49	0.95	(0.82, 1.10)	-0.0535	0.0451	2.36E-01	1.00E+00
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	0.99	(0.81, 1.21)	-0.0084	0.0610	8.90E-01	1.00E+00
GENETIC ANCESTRY						
Admixed African-European	1.23	(0.94, 1.62)	0.2084	0.0848	1.40E-02	5.89E-01
European	1.00		0.0000		nan	nan
Admixed Amerindian	1.32	(1.08, 1.62)	0.2810	0.0621	6.13E-06	2.57E-04
Other	1.10	(0.93, 1.29)	0.0923	0.0504	6.73E-02	1.00E+00
EXPOSURE						
Any	8.72	(7.42, 10.26)	2.1659	0.0501	0.00E+00	0.00E+00
Biological relative tested positive	5.77	(4.99, 6.68)	1.7529	0.0450	0.00E+00	0.00E+00
Directly exposed to someone who tested positive	6.94	(6.02, 7.99)	1.9366	0.0438	0.00E+00	0.00E+00
Healthcare worker directly exposed	1.44	(1.26, 1.65)	0.3670	0.0408	2.31E-19	9.69E-18
Household member tested positive	26.03	(22.26, 30.43)	3.2591	0.0482	0.00E+00	0.00E+00
HEALTH CONDITIONS						
Asthma	0.78	(0.66, 0.93)	-0.2450	0.0519	2.37E-06	9.95E-05
COPD (Chronic Obstructive Pulmonary Disease)	0.85	(0.57, 1.29)	-0.1571	0.1276	2.18E-01	1.00E+00
Cancer treated in the past year	0.83	(0.51, 1.34)	-0.1884	0.1480	2.03E-01	1.00E+00
Cardiovascular disease	0.96	(0.71, 1.29)	-0.0436	0.0920	6.36E-01	1.00E+00
Chronic kidney disease	0.77	(0.43, 1.37)	-0.2656	0.1784	1.37E-01	1.00E+00
Diabetes	1.09	(0.88, 1.35)	0.0886	0.0657	1.78E-01	1.00E+00
Hypertension	0.90	(0.77, 1.05)	-0.1034	0.0479	3.08E-02	1.00E+00
Other	0.97	(0.75, 1.25)	-0.0293	0.0788	7.11E-01	1.00E+00
Other autoimmune disease	0.82	(0.67, 1.00)	-0.2042	0.0628	1.15E-03	4.85E-02
Other immunodeficiency disorder	0.69	(0.43, 1.11)	-0.3735	0.1482	1.18E-02	4.94E-01

Other lung condition	0.66	(0.44, 0.99)	-0.4166	0.1242	7.99E-04	3.36E-02
Any	0.80	(0.70, 0.91)	-0.2243	0.0391	9.55E-09	4.01E-07
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	0.99	(0.84, 1.17)	-0.0079	0.0500	8.75E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.04	(0.84, 1.28)	0.0348	0.0647	5.90E-01	1.00E+00
obesity III (BMI >= 40)	0.99	(0.79, 1.26)	-0.0056	0.0719	9.38E-01	1.00E+00
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	1.35	(1.18, 1.54)	0.2989	0.0408	2.46E-13	1.04E-11
SYMPTOMS						
Abdominal pain	0.96	(0.68, 1.38)	-0.0364	0.1100	7.41E-01	1.00E+00
Body aches	1.27	(0.94, 1.73)	0.2429	0.0934	9.31E-03	3.91E-01
Change in taste or smell	6.43	(4.59, 9.00)	1.8607	0.1039	1.18E-71	4.94E-70
Chills	1.36	(1.01, 1.82)	0.3073	0.0908	7.11E-04	2.99E-02
Cough producing phlegm	0.89	(0.64, 1.22)	-0.1208	0.0981	2.18E-01	1.00E+00
Diarrhea	1.13	(0.83, 1.55)	0.1258	0.0963	1.92E-01	1.00E+00
Dry cough	1.02	(0.76, 1.37)	0.0243	0.0906	7.88E-01	1.00E+00
Feeling tired or fatigue	1.27	(0.87, 1.86)	0.2389	0.1181	4.31E-02	1.00E+00
Fever	1.53	(1.14, 2.06)	0.4276	0.0911	2.67E-06	1.12E-04
Headache	1.01	(0.74, 1.37)	0.0092	0.0951	9.23E-01	1.00E+00
Nasal congestion	0.69	(0.51, 0.92)	-0.3766	0.0909	3.45E-05	1.45E-03
Nausea or vomiting	0.92	(0.64, 1.33)	-0.0808	0.1122	4.71E-01	1.00E+00
Runny nose	0.56	(0.41, 0.76)	-0.5841	0.0954	9.02E-10	3.79E-08
Shortness of breath	1.26	(0.93, 1.70)	0.2286	0.0926	1.35E-02	5.68E-01
Sore throat	0.46	(0.34, 0.63)	-0.7711	0.0940	2.22E-16	9.33E-15

Adjusted odds ratios for a positive COVID-19 test were calculated among survey participants reporting a test result (positive or negative) based on the self-reported response to the following question: “Have you been swab tested for COVID-19, commonly referred to as coronavirus?” The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among

577 symptomatic customers only (Methods). Here, odds ratios were adjusted for four known
578 exposures (Y/N if any).
579

580 **Supplementary Table 9. Risk factor odds ratios for COVID-19 susceptibility, adjusted for**
581 **exposure, age, and sex**
582

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.28	(1.03, 1.59)	0.2448	0.0672	2.72E-04	1.14E-02
Ages 30-49	0.94	(0.81, 1.09)	-0.0583	0.0453	1.97E-01	1.00E+00
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	0.96	(0.79, 1.18)	-0.0372	0.0613	5.44E-01	1.00E+00
GENETIC ANCESTRY						
Admixed African-European	1.23	(0.94, 1.62)	0.2091	0.0852	1.42E-02	5.95E-01
European	1.00		0.0000		nan	nan
Admixed Amerindian	1.27	(1.04, 1.57)	0.2417	0.0636	1.46E-04	6.11E-03
Other	1.09	(0.92, 1.29)	0.0863	0.0509	8.98E-02	1.00E+00
EXPOSURE						
Any	8.63	(7.31, 10.19)	2.1555	0.0512	0.00E+00	0.00E+00
Biological relative tested positive	5.68	(4.90, 6.58)	1.7372	0.0455	0.00E+00	0.00E+00
Directly exposed to someone who tested positive	6.71	(5.80, 7.76)	1.9034	0.0451	0.00E+00	0.00E+00
Healthcare worker directly exposed	1.33	(1.16, 1.52)	0.2823	0.0420	1.75E-11	7.34E-10
Household member tested positive	25.09	(21.44, 29.36)	3.2224	0.0485	0.00E+00	0.00E+00
HEALTH CONDITIONS						
Asthma	0.82	(0.69, 0.97)	-0.2045	0.0524	9.47E-05	3.98E-03
COPD (Chronic Obstructive Pulmonary Disease)	0.88	(0.58, 1.34)	-0.1281	0.1290	3.21E-01	1.00E+00
Cancer treated in the past year	0.83	(0.51, 1.34)	-0.1877	0.1488	2.07E-01	1.00E+00
Cardiovascular disease	0.94	(0.69, 1.28)	-0.0598	0.0944	5.27E-01	1.00E+00
Chronic kidney disease	0.78	(0.44, 1.40)	-0.2475	0.1791	1.67E-01	1.00E+00
Diabetes	1.10	(0.88, 1.36)	0.0922	0.0673	1.71E-01	1.00E+00
Hypertension	0.90	(0.76, 1.05)	-0.1097	0.0499	2.80E-02	1.00E+00
Other	0.99	(0.77, 1.28)	-0.0080	0.0790	9.20E-01	1.00E+00
Other autoimmune disease	0.87	(0.71, 1.07)	-0.1382	0.0636	2.97E-02	1.00E+00
Other immunodeficiency disorder	0.69	(0.42, 1.11)	-0.3764	0.1496	1.19E-02	4.99E-01

Other lung condition	0.67	(0.44, 1.00)	-0.4064	0.1248	1.13E-03	4.76E-02
Any	0.81	(0.71, 0.92)	-0.2092	0.0405	2.32E-07	9.76E-06
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	0.99	(0.84, 1.16)	-0.0113	0.0502	8.23E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.04	(0.84, 1.28)	0.0390	0.0649	5.47E-01	1.00E+00
obesity III (BMI >= 40)	1.01	(0.80, 1.28)	0.0097	0.0724	8.94E-01	1.00E+00
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	1.36	(1.19, 1.55)	0.3039	0.0409	1.09E-13	4.57E-12
SYMPTOMS						
Abdominal pain	1.00	(0.70, 1.44)	0.0048	0.1108	9.65E-01	1.00E+00
Body aches	1.29	(0.95, 1.74)	0.2508	0.0941	7.72E-03	3.24E-01
Change in taste or smell	6.68	(4.75, 9.39)	1.8991	0.1052	6.77E-73	2.84E-71
Chills	1.35	(1.01, 1.82)	0.3014	0.0912	9.56E-04	4.02E-02
Cough producing phlegm	0.90	(0.65, 1.23)	-0.1098	0.0986	2.65E-01	1.00E+00
Diarrhea	1.16	(0.85, 1.59)	0.1522	0.0970	1.17E-01	1.00E+00
Dry cough	1.05	(0.78, 1.40)	0.0442	0.0912	6.28E-01	1.00E+00
Feeling tired or fatigue	1.35	(0.92, 2.00)	0.3029	0.1202	1.17E-02	4.91E-01
Fever	1.52	(1.13, 2.05)	0.4189	0.0916	4.76E-06	2.00E-04
Headache	1.02	(0.74, 1.40)	0.0218	0.0977	8.24E-01	1.00E+00
Nasal congestion	0.69	(0.52, 0.93)	-0.3651	0.0918	6.93E-05	2.91E-03
Nausea or vomiting	0.96	(0.67, 1.38)	-0.0401	0.1128	7.22E-01	1.00E+00
Runny nose	0.57	(0.42, 0.77)	-0.5690	0.0958	2.83E-09	1.19E-07
Shortness of breath	1.30	(0.96, 1.76)	0.2607	0.0934	5.22E-03	2.19E-01
Sore throat	0.47	(0.34, 0.64)	-0.7609	0.0951	1.33E-15	5.60E-14

Adjusted odds ratios for a positive COVID-19 test were calculated among survey participants reporting a test result (positive or negative) based on the self-reported response to the following question: “Have you been swab tested for COVID-19, commonly referred to as coronavirus?” The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among

symptomatic customers only (Methods). Here, odds ratios were adjusted for four known exposures (Y/N if any), age, and genetic sex (Supplementary Table 2 and Methods).

Supplementary Table 10. Unadjusted risk factor odds ratios for a known "direct" COVID-19 exposure

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.80	(1.54, 2.12)	0.5896	0.0519	6.64E-30	1.66E-28
Ages 30-49	1.45	(1.31, 1.60)	0.3725	0.0325	2.00E-30	5.00E-29
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	0.32	(0.28, 0.37)	-1.1427	0.0437	0.00E+00	0.00E+00
GENETIC ANCESTRY						
Admixed African-European	1.49	(1.23, 1.82)	0.4012	0.0639	3.32E-10	8.31E-09
European	1.00		0.0000		nan	nan
Admixed Amerindian	1.40	(1.21, 1.62)	0.3384	0.0476	1.13E-12	2.82E-11
Other	1.17	(1.05, 1.31)	0.1584	0.0365	1.47E-05	3.67E-04
EXPOSURE						
Biological relative tested positive	4.43	(3.79, 5.18)	1.4888	0.0503	1.39E-192	3.48E-191
Healthcare worker directly exposed	11.53	(10.16, 13.08)	2.4450	0.0408	0.00E+00	0.00E+00
Household member tested positive	22.53	(17.88, 28.38)	3.1148	0.0747	0.00E+00	0.00E+00
HEALTH CONDITIONS						
Asthma	1.02	(0.92, 1.14)	0.0216	0.0353	5.40E-01	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	0.44	(0.33, 0.57)	-0.8297	0.0875	0.00E+00	0.00E+00
Cancer treated in the past year	0.36	(0.26, 0.49)	-1.0310	0.1012	0.00E+00	0.00E+00
Cardiovascular disease	0.50	(0.41, 0.61)	-0.6880	0.0647	0.00E+00	0.00E+00
Chronic kidney disease	0.39	(0.27, 0.57)	-0.9295	0.1182	3.77E-15	9.44E-14
Diabetes	0.63	(0.54, 0.73)	-0.4656	0.0473	0.00E+00	0.00E+00
Hypertension	0.73	(0.66, 0.81)	-0.3181	0.0332	0.00E+00	0.00E+00
Other	0.99	(0.84, 1.18)	-0.0080	0.0556	8.86E-01	1.00E+00
Other autoimmune disease	0.87	(0.76, 0.99)	-0.1421	0.0424	8.06E-04	2.02E-02
Other immunodeficiency disorder	0.87	(0.65, 1.17)	-0.1389	0.0953	1.45E-01	1.00E+00
Other lung condition	0.62	(0.48, 0.78)	-0.4859	0.0778	4.22E-10	1.05E-08
Any	0.71	(0.65, 0.78)	-0.3393	0.0276	0.00E+00	0.00E+00

OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.03	(0.93, 1.15)	0.0338	0.0350	3.35E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.03	(0.90, 1.19)	0.0343	0.0456	4.52E-01	1.00E+00
obesity III (BMI >= 40)	1.10	(0.94, 1.28)	0.0927	0.0499	6.31E-02	1.00E+00
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	0.96	(0.87, 1.05)	-0.0443	0.0295	1.33E-01	1.00E+00

Unadjusted odds ratios for a known “direct” exposure to COVID-19 were calculated based on the self-reported response to the following question: “Have you been directly exposed to someone who has tested positive for COVID-19?” The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity).

617 **Supplementary Table 11. Unadjusted risk factor odds ratios for a household case(s) of**
618 **COVID-19**

619

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.44	(1.15, 1.79)	0.3623	0.0715	4.01E-07	1.00E-05
Ages 30-49	0.98	(0.84, 1.14)	-0.0204	0.0488	6.76E-01	1.00E+00
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	0.50	(0.41, 0.61)	-0.6882	0.0641	0.00E+00	0.00E+00
GENETIC ANCESTRY						
Admixed African-European	1.35	(1.00, 1.81)	0.2971	0.0954	1.84E-03	4.60E-02
European	1.00		0.0000		nan	nan
Admixed Amerindian	1.95	(1.60, 2.37)	0.6686	0.0634	5.56E-26	1.39E-24
Other	1.23	(1.04, 1.47)	0.2107	0.0557	1.56E-04	3.90E-03
EXPOSURE						
Biological relative tested positive	14.32	(12.30, 16.67)	2.6615	0.0491	0.00E+00	0.00E+00
Directly exposed to someone who tested positive	22.53	(17.88, 28.38)	3.1148	0.0747	0.00E+00	0.00E+00
Healthcare worker directly exposed	1.11	(0.94, 1.32)	0.1073	0.0540	4.71E-02	1.00E+00
HEALTH CONDITIONS						
Asthma	0.91	(0.77, 1.07)	-0.0975	0.0549	7.59E-02	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	0.58	(0.38, 0.89)	-0.5405	0.1363	7.31E-05	1.83E-03
Cancer treated in the past year	0.44	(0.26, 0.75)	-0.8217	0.1735	2.19E-06	5.48E-05
Cardiovascular disease	0.68	(0.50, 0.93)	-0.3795	0.0988	1.23E-04	3.07E-03
Chronic kidney disease	0.53	(0.30, 0.97)	-0.6255	0.1911	1.06E-03	2.66E-02
Diabetes	0.89	(0.72, 1.10)	-0.1187	0.0701	9.02E-02	1.00E+00
Hypertension	0.80	(0.69, 0.94)	-0.2182	0.0516	2.31E-05	5.77E-04
Other	0.93	(0.72, 1.21)	-0.0673	0.0845	4.26E-01	1.00E+00
Other autoimmune disease	0.85	(0.69, 1.04)	-0.1684	0.0667	1.16E-02	2.90E-01
Other immunodeficiency disorder	0.87	(0.56, 1.37)	-0.1357	0.1453	3.50E-01	1.00E+00
Other lung condition	0.63	(0.42, 0.94)	-0.4620	0.1292	3.48E-04	8.70E-03
Any	0.74	(0.65, 0.84)	-0.3047	0.0423	5.80E-13	1.45E-11

OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.05	(0.89, 1.23)	0.0460	0.0533	3.88E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.01	(0.81, 1.25)	0.0064	0.0704	9.28E-01	1.00E+00
obesity III (BMI >= 40)	1.04	(0.82, 1.32)	0.0374	0.0769	6.27E-01	1.00E+00
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	1.18	(1.03, 1.36)	0.1688	0.0438	1.16E-04	2.89E-03

Unadjusted odds ratios for a household case(s) of COVID-19 were calculated based on the self-reported response to the following question: “Has someone in your household tested positive for COVID-19?” The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity).

639 **Supplementary Table 12. Unadjusted risk factor odds ratios for a COVID-19 case(s)**
640 **amongst close biological relatives (parent, grandparent, child, or sibling)**

641

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.48	(1.18, 1.86)	0.3934	0.0730	7.16E-08	1.79E-06
Ages 30-49	1.02	(0.88, 1.19)	0.0222	0.0502	6.59E-01	1.00E+00
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	0.70	(0.58, 0.85)	-0.3523	0.0605	5.90E-09	1.47E-07
GENETIC ANCESTRY						
Admixed African-European	1.69	(1.28, 2.22)	0.5221	0.0896	5.62E-09	1.41E-07
European	1.00		0.0000		nan	nan
Admixed Amerindian	2.08	(1.71, 2.53)	0.7333	0.0634	5.85E-31	1.46E-29
Other	1.42	(1.20, 1.68)	0.3472	0.0547	2.14E-10	5.34E-09
EXPOSURE						
Directly exposed to someone who tested positive	4.43	(3.79, 5.18)	1.4888	0.0503	1.39E-192	3.48E-191
Healthcare worker directly exposed	1.04	(0.87, 1.23)	0.0384	0.0558	4.91E-01	1.00E+00
Household member tested positive	14.32	(12.30, 16.67)	2.6615	0.0491	0.00E+00	0.00E+00
HEALTH CONDITIONS						
Asthma	0.98	(0.82, 1.16)	-0.0245	0.0547	6.54E-01	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	0.68	(0.46, 1.02)	-0.3791	0.1293	3.37E-03	8.42E-02
Cancer treated in the past year	0.60	(0.37, 0.97)	-0.5105	0.1542	9.33E-04	2.33E-02
Cardiovascular disease	0.77	(0.57, 1.04)	-0.2600	0.0959	6.72E-03	1.68E-01
Chronic kidney disease	0.52	(0.28, 0.95)	-0.6619	0.1977	8.12E-04	2.03E-02
Diabetes	1.04	(0.84, 1.28)	0.0368	0.0677	5.86E-01	1.00E+00
Hypertension	0.88	(0.75, 1.03)	-0.1281	0.0513	1.25E-02	3.12E-01
Other	1.03	(0.80, 1.33)	0.0297	0.0829	7.20E-01	1.00E+00
Other autoimmune disease	0.90	(0.73, 1.10)	-0.1057	0.0663	1.11E-01	1.00E+00
Other immunodeficiency disorder	0.99	(0.65, 1.53)	-0.0065	0.1394	9.63E-01	1.00E+00
Other lung condition	0.96	(0.69, 1.36)	-0.0368	0.1104	7.39E-01	1.00E+00
Any	0.85	(0.74, 0.97)	-0.1668	0.0429	1.02E-04	2.55E-03

OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.03	(0.87, 1.22)	0.0327	0.0541	5.45E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	0.88	(0.70, 1.11)	-0.1292	0.0748	8.41E-02	1.00E+00
obesity III (BMI >= 40)	1.10	(0.87, 1.39)	0.0945	0.0761	2.14E-01	1.00E+00
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	0.87	(0.75, 1.00)	-0.1404	0.0462	2.39E-03	5.99E-02

Unadjusted odds ratios for a case(s) of COVID-19 among close biological relatives (grandparent, parent, child, or sibling) were calculated based on the self-reported response to the following question: “Have any of your biological relatives tested positive for COVID-19? Select all that apply.” The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity).

662 **Supplementary Table 13. Unadjusted risk factor odds ratios for COVID-19 hospitalization**
663

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	0.42	(0.21, 0.83)	-0.8793	0.2143	4.06E-05	1.71E-03
Ages 30-49	0.54	(0.36, 0.81)	-0.6143	0.1246	8.24E-07	3.46E-05
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	1.70	(1.13, 2.56)	0.5325	0.1263	2.49E-05	1.05E-03
GENETIC ANCESTRY						
Admixed African-European	1.44	(0.78, 2.65)	0.3625	0.1884	5.43E-02	1.00E+00
European	1.00		0.0000		nan	nan
Admixed Amerindian	0.77	(0.44, 1.36)	-0.2579	0.1745	1.39E-01	1.00E+00
Other	0.91	(0.59, 1.40)	-0.0964	0.1335	4.70E-01	1.00E+00
EXPOSURE						
Any	0.74	(0.46, 1.19)	-0.3048	0.1483	3.98E-02	1.00E+00
Biological relative tested positive	1.17	(0.81, 1.69)	0.1550	0.1136	1.73E-01	1.00E+00
Directly exposed to someone who tested positive	0.63	(0.42, 0.96)	-0.4595	0.1279	3.28E-04	1.38E-02
Healthcare worker directly exposed	0.53	(0.34, 0.84)	-0.6317	0.1423	9.09E-06	3.82E-04
Household member tested positive	0.91	(0.65, 1.27)	-0.0971	0.1033	3.47E-01	1.00E+00
HEALTH CONDITIONS						
Asthma	1.42	(0.95, 2.13)	0.3525	0.1249	4.77E-03	2.00E-01
COPD (Chronic Obstructive Pulmonary Disease)	3.48	(1.65, 7.32)	1.2469	0.2296	5.64E-08	2.37E-06
Cancer treated in the past year	3.13	(1.29, 7.57)	1.1396	0.2730	2.99E-05	1.26E-03
Cardiovascular disease	2.82	(1.61, 4.96)	1.0374	0.1740	2.50E-09	1.05E-07
Chronic kidney disease	8.74	(3.44, 22.21)	2.1684	0.2876	4.71E-14	1.98E-12
Diabetes	3.03	(1.98, 4.63)	1.1085	0.1311	2.78E-17	1.17E-15
Hypertension	2.01	(1.41, 2.88)	0.7002	0.1105	2.37E-10	9.96E-09
Other	1.65	(0.93, 2.93)	0.5038	0.1767	4.35E-03	1.83E-01
Other autoimmune disease	1.32	(0.81, 2.17)	0.2811	0.1523	6.49E-02	1.00E+00
Other immunodeficiency disorder	1.98	(0.77, 5.09)	0.6826	0.2915	1.92E-02	8.05E-01
Other lung condition	2.84	(1.32, 6.10)	1.0423	0.2364	1.04E-05	4.35E-04

Any	2.70	(1.90, 3.83)	0.9919	0.1081	4.43E-20	1.86E-18
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.41	(0.94, 2.12)	0.3418	0.1258	6.61E-03	2.78E-01
obesity II (BMI >= 35 and BMI < 40)	1.21	(0.70, 2.09)	0.1883	0.1693	2.66E-01	1.00E+00
obesity III (BMI >= 40)	1.62	(0.93, 2.83)	0.4820	0.1719	5.04E-03	2.12E-01
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	1.27	(0.92, 1.77)	0.2418	0.1015	1.72E-02	7.22E-01
SYMPTOMS						
Abdominal pain	1.76	(1.23, 2.52)	0.5638	0.1112	3.92E-07	1.65E-05
Body aches	1.39	(0.96, 2.02)	0.3309	0.1142	3.75E-03	1.57E-01
Change in taste or smell	0.77	(0.55, 1.07)	-0.2657	0.1039	1.05E-02	4.42E-01
Chills	1.82	(1.29, 2.57)	0.5991	0.1061	1.65E-08	6.92E-07
Cough producing phlegm	1.56	(1.11, 2.20)	0.4474	0.1054	2.19E-05	9.18E-04
Diarrhea	2.12	(1.52, 2.95)	0.7521	0.1021	1.75E-13	7.35E-12
Dry cough	2.59	(1.81, 3.71)	0.9528	0.1104	6.26E-18	2.63E-16
Feeling tired or fatigue	2.54	(1.35, 4.78)	0.9335	0.1949	1.68E-06	7.04E-05
Fever	3.33	(2.26, 4.90)	1.2032	0.1192	5.93E-24	2.49E-22
Headache	0.89	(0.63, 1.26)	-0.1125	0.1063	2.90E-01	1.00E+00
Nasal congestion	0.94	(0.67, 1.31)	-0.0610	0.1030	5.54E-01	1.00E+00
Nausea or vomiting	2.26	(1.58, 3.23)	0.8156	0.1104	1.52E-13	6.39E-12
Runny nose	1.09	(0.76, 1.56)	0.0831	0.1118	4.57E-01	1.00E+00
Shortness of breath	7.52	(4.92, 11.49)	2.0172	0.1309	1.48E-53	6.21E-52
Sore throat	1.04	(0.72, 1.50)	0.0386	0.1127	7.32E-01	1.00E+00

Unadjusted odds ratios for hospitalization due to COVID-19 infection were calculated among those reporting a positive COVID-19 test result. The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods).

671 **Supplementary Table 14. Risk factor odds ratios for COVID-19 hospitalization, adjusted**
672 **for health conditions, obesity, age, and sex**
673

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	0.56	(0.26, 1.20)	-0.5815	0.2359	1.37E-02	5.75E-01
Ages 30-49	0.60	(0.39, 0.92)	-0.5110	0.1333	1.26E-04	5.28E-03
Ages 50-64	1.00		0.0000		nan	nan
Ages 65+	1.60	(1.02, 2.51)	0.4713	0.1381	6.43E-04	2.70E-02
GENETIC ANCESTRY						
Admixed African-European	1.57	(0.81, 3.03)	0.4513	0.2026	2.59E-02	1.00E+00
European	1.00		0.0000		nan	nan
Admixed Amerindian	1.11	(0.59, 2.07)	0.1035	0.1922	5.90E-01	1.00E+00
Other	0.95	(0.59, 1.54)	-0.0493	0.1490	7.41E-01	1.00E+00
EXPOSURE						
Any	0.81	(0.48, 1.39)	-0.2060	0.1653	2.13E-01	1.00E+00
Biological relative tested positive	1.16	(0.78, 1.74)	0.1498	0.1248	2.30E-01	1.00E+00
Directly exposed to someone who tested positive	0.68	(0.43, 1.07)	-0.3870	0.1397	5.61E-03	2.36E-01
Healthcare worker directly exposed	0.63	(0.38, 1.04)	-0.4685	0.1567	2.79E-03	1.17E-01
Household member tested positive	0.88	(0.62, 1.26)	-0.1245	0.1109	2.62E-01	1.00E+00
HEALTH CONDITIONS						
Asthma	1.42	(0.92, 2.20)	0.3537	0.1343	8.42E-03	3.54E-01
COPD (Chronic Obstructive Pulmonary Disease)	2.25	(0.99, 5.14)	0.8123	0.2542	1.40E-03	5.87E-02
Cancer treated in the past year	1.90	(0.72, 5.04)	0.6422	0.3012	3.30E-02	1.00E+00
Cardiovascular disease	1.67	(0.90, 3.11)	0.5139	0.1914	7.24E-03	3.04E-01
Chronic kidney disease	5.62	(2.10, 15.03)	1.7267	0.3034	1.26E-08	5.30E-07
Diabetes	2.22	(1.39, 3.55)	0.7988	0.1442	3.06E-08	1.28E-06
Hypertension	1.32	(0.88, 1.97)	0.2757	0.1239	2.61E-02	1.00E+00
Other	1.47	(0.80, 2.71)	0.3878	0.1875	3.86E-02	1.00E+00
Other autoimmune disease	1.41	(0.83, 2.40)	0.3461	0.1635	3.42E-02	1.00E+00
Other immunodeficiency disorder	1.83	(0.68, 4.93)	0.6032	0.3062	4.88E-02	1.00E+00

Other lung condition	1.87	(0.83, 4.22)	0.6242	0.2514	1.30E-02	5.47E-01
Any	2.08	(1.42, 3.04)	0.7333	0.1172	3.93E-10	1.65E-08
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.19	(0.77, 1.82)	0.1707	0.1323	1.97E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.13	(0.64, 2.00)	0.1249	0.1750	4.75E-01	1.00E+00
obesity III (BMI >= 40)	1.59	(0.88, 2.87)	0.4631	0.1821	1.10E-02	4.62E-01
Not obese	1.00		0.0000		nan	nan
GENETIC SEX						
Female	1.00		0.0000		nan	nan
Male	1.22	(0.85, 1.74)	0.1960	0.1103	7.57E-02	1.00E+00
SYMPTOMS						
Abdominal pain	1.66	(1.12, 2.46)	0.5086	0.1214	2.81E-05	1.18E-03
Body aches	1.44	(0.96, 2.15)	0.3646	0.1240	3.27E-03	1.37E-01
Change in taste or smell	0.89	(0.62, 1.29)	-0.1159	0.1139	3.09E-01	1.00E+00
Chills	1.94	(1.33, 2.82)	0.6609	0.1156	1.07E-08	4.51E-07
Cough producing phlegm	1.41	(0.97, 2.05)	0.3470	0.1150	2.54E-03	1.07E-01
Diarrhea	2.23	(1.55, 3.20)	0.8014	0.1120	8.21E-13	3.45E-11
Dry cough	2.49	(1.69, 3.67)	0.9114	0.1196	2.55E-14	1.07E-12
Feeling tired or fatigue	2.81	(1.38, 5.74)	1.0333	0.2203	2.73E-06	1.15E-04
Fever	3.49	(2.29, 5.34)	1.2510	0.1309	1.24E-21	5.19E-20
Headache	1.05	(0.72, 1.54)	0.0487	0.1180	6.80E-01	1.00E+00
Nasal congestion	0.93	(0.65, 1.34)	-0.0698	0.1122	5.34E-01	1.00E+00
Nausea or vomiting	2.41	(1.62, 3.59)	0.8801	0.1230	8.38E-13	3.52E-11
Runny nose	0.93	(0.62, 1.39)	-0.0710	0.1232	5.65E-01	1.00E+00
Shortness of breath	8.20	(5.14, 13.08)	2.1042	0.1440	2.37E-48	9.96E-47
Sore throat	1.11	(0.75, 1.66)	0.1074	0.1224	3.80E-01	1.00E+00

Adjusted odds ratios for hospitalization due to COVID-19 infection were calculated among those reporting a positive COVID-19 test result. The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods). Here, odds ratios were adjusted for age, sex, comorbitidies (Y/N if any), and obesity (Y/N if BMI > 30, Methods).

683 **Supplementary Table 15. Unadjusted risk factor odds ratios for progression of COVID-19**
684 **to a critical case.**
685

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	0.35	(0.13, 0.95)	-1.0599	0.3114	6.64E-04	2.79E-02
Ages 30-49	0.55	(0.32, 0.94)	-0.5983	0.1652	2.92E-04	1.23E-02
Ages 50-64	1		0		nan	nan
Ages 65+	1.65	(0.97, 2.80)	0.5001	0.1632	2.19E-03	9.18E-02
GENETIC ANCESTRY						
Admixed African-European	2.07	(1.03, 4.17)	0.7269	0.2166	7.91E-04	3.32E-02
European	1		0		nan	nan
Admixed Amerindian	0.75	(0.35, 1.62)	-0.2871	0.2377	2.27E-01	1.00E+00
Other	0.82	(0.45, 1.49)	-0.2044	0.1853	2.70E-01	1.00E+00
EXPOSURE						
Any	0.77	(0.40, 1.45)	-0.2675	0.1981	1.77E-01	1.00E+00
Biological relative tested positive	1.15	(0.70, 1.86)	0.1356	0.1502	3.67E-01	1.00E+00
Directly exposed to someone who tested positive	0.59	(0.34, 1.01)	-0.5348	0.1691	1.56E-03	6.55E-02
Healthcare worker directly exposed	0.53	(0.29, 0.99)	-0.6277	0.1912	1.03E-03	4.31E-02
Household member tested positive	1.00	(0.64, 1.55)	-0.0001	0.1353	1.00E+00	1.00E+00
HEALTH CONDITIONS						
Asthma	1.26	(0.74, 2.17)	0.235	0.1672	1.60E-01	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	3.76	(1.57, 9.02)	1.3257	0.2696	8.79E-07	3.69E-05
Cancer treated in the past year	2.07	(0.60, 7.12)	0.7266	0.3814	5.68E-02	1.00E+00
Cardiovascular disease	2.44	(1.17, 5.05)	0.8906	0.2251	7.60E-05	3.19E-03
Chronic kidney disease	8.00	(2.92, 21.91)	2.0794	0.3109	2.26E-11	9.47E-10
Diabetes	3.14	(1.85, 5.32)	1.1431	0.1629	2.29E-12	9.61E-11
Hypertension	2.06	(1.30, 3.27)	0.7214	0.1425	4.15E-07	1.74E-05
Other	1.07	(0.45, 2.54)	0.0649	0.2674	8.08E-01	1.00E+00
Other autoimmune disease	1.35	(0.71, 2.55)	0.2973	0.1973	1.32E-01	1.00E+00
Other immunodeficiency disorder	1.81	(0.53, 6.16)	0.5907	0.3788	1.19E-01	1.00E+00

Other lung condition	3.29	(1.35, 8.00)	1.1909	0.274	1.39E-05	5.82E-04
Any	2.85	(1.78, 4.57)	1.0485	0.1452	5.22E-13	2.19E-11
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.31	(0.76, 2.27)	0.2714	0.1696	1.09E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.16	(0.56, 2.43)	0.1525	0.2275	5.03E-01	1.00E+00
obesity III (BMI >= 40)	2.06	(1.05, 4.02)	0.7211	0.2071	4.98E-04	2.09E-02
Not obese	1		0		nan	nan
GENETIC SEX						
Female	1		0		nan	nan
Male	1.54	(1.00, 2.37)	0.4342	0.1325	1.05E-03	4.42E-02
SYMPTOMS						
Abdominal pain	1.95	(1.23, 3.08)	0.666	0.1413	2.45E-06	1.03E-04
Body aches	1.58	(0.95, 2.60)	0.4547	0.1546	3.27E-03	1.37E-01
Change in taste or smell	0.79	(0.51, 1.23)	-0.2319	0.1358	8.79E-02	1.00E+00
Chills	2.04	(1.28, 3.23)	0.7106	0.1423	5.96E-07	2.50E-05
Cough producing phlegm	1.83	(1.18, 2.84)	0.6063	0.1351	7.24E-06	3.04E-04
Diarrhea	2.48	(1.61, 3.84)	0.9102	0.1339	1.08E-11	4.53E-10
Dry cough	2.67	(1.66, 4.31)	0.9836	0.1474	2.49E-11	1.04E-09
Feeling tired or fatigue	2.55	(1.09, 5.97)	0.9344	0.2628	3.77E-04	1.58E-02
Fever	3.52	(2.08, 5.96)	1.2595	0.1622	8.00E-15	3.36E-13
Headache	0.97	(0.61, 1.52)	-0.0356	0.1402	8.00E-01	1.00E+00
Nasal congestion	1.06	(0.69, 1.64)	0.0592	0.1337	6.58E-01	1.00E+00
Nausea or vomiting	2.27	(1.44, 3.60)	0.8217	0.1415	6.30E-09	2.64E-07
Runny nose	1.31	(0.83, 2.07)	0.2696	0.1415	5.68E-02	1.00E+00
Shortness of breath	11.55	(5.91, 22.59)	2.4466	0.2069	2.93E-32	1.23E-30
Sore throat	1.45	(0.92, 2.29)	0.374	0.1396	7.40E-03	3.11E-01

Unadjusted odds ratios for progression of COVID-19 infection to a critical, life-threatening illness were calculated among those reporting a positive COVID-19 test result. The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods).

694 **Supplementary Table 16. Risk factor odds ratios for progression of COVID-19 to a critical**
695 **case, adjusted for health conditions, obesity, age, and sex.**

696

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	0.46	(0.15, 1.45)	-0.7675	0.3506	2.86E-02	1.00E+00
Ages 30-49	0.67	(0.38, 1.17)	-0.4033	0.1735	2.01E-02	8.45E-01
Ages 50-64	1		0		nan	nan
Ages 65+	1.51	(0.85, 2.69)	0.41	0.1785	2.16E-02	9.07E-01
GENETIC ANCESTRY						
Admixed African-European	2.34	(1.11, 4.95)	0.8516	0.2308	2.25E-04	9.43E-03
European	1		0		nan	nan
Admixed Amerindian	1.12	(0.49, 2.56)	0.1145	0.2548	6.53E-01	1.00E+00
Other	0.85	(0.44, 1.65)	-0.164	0.206	4.26E-01	1.00E+00
EXPOSURE						
Any	0.83	(0.41, 1.67)	-0.1862	0.2163	3.89E-01	1.00E+00
Biological relative tested positive	1.23	(0.73, 2.08)	0.2104	0.1609	1.91E-01	1.00E+00
Directly exposed to someone who tested positive	0.62	(0.34, 1.13)	-0.4747	0.183	9.49E-03	3.98E-01
Healthcare worker directly exposed	0.62	(0.31, 1.24)	-0.4703	0.2116	2.63E-02	1.00E+00
Household member tested positive	1.01	(0.63, 1.60)	0.0068	0.1434	9.62E-01	1.00E+00
HEALTH CONDITIONS						
Asthma	1.24	(0.69, 2.22)	0.2124	0.1806	2.40E-01	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	2.39	(0.90, 6.36)	0.8704	0.302	3.95E-03	1.66E-01
Cancer treated in the past year	1.08	(0.26, 4.55)	0.0784	0.4429	8.59E-01	1.00E+00
Cardiovascular disease	1.42	(0.64, 3.15)	0.3485	0.2469	1.58E-01	1.00E+00
Chronic kidney disease	4.88	(1.67, 14.30)	1.586	0.3314	1.70E-06	7.13E-05
Diabetes	2.16	(1.20, 3.89)	0.7699	0.1816	2.23E-05	9.38E-04
Hypertension	1.34	(0.80, 2.24)	0.2903	0.1599	6.95E-02	1.00E+00
Other	1.19	(0.49, 2.88)	0.1765	0.2714	5.16E-01	1.00E+00
Other autoimmune disease	1.55	(0.78, 3.06)	0.4368	0.2105	3.80E-02	1.00E+00
Other immunodeficiency disorder	1.82	(0.52, 6.31)	0.5962	0.3844	1.21E-01	1.00E+00

Other lung condition	2.09	(0.80, 5.47)	0.7376	0.2965	1.29E-02	5.40E-01
Any	2.22	(1.33, 3.69)	0.7959	0.157	4.00E-07	1.68E-05
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.09	(0.62, 1.93)	0.0882	0.1761	6.17E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.06	(0.50, 2.26)	0.0605	0.2334	7.96E-01	1.00E+00
obesity III (BMI >= 40)	1.95	(0.96, 3.98)	0.6695	0.2196	2.29E-03	9.64E-02
Not obese	1		0		nan	nan
GENETIC SEX						
Female	1		0		nan	nan
Male	1.5	(0.95, 2.37)	0.4041	0.142	4.42E-03	1.85E-01
SYMPTOMS						
Abdominal pain	2.03	(1.24, 3.32)	0.7095	0.1514	2.77E-06	1.16E-04
Body aches	1.88	(1.08, 3.27)	0.6321	0.1707	2.13E-04	8.95E-03
Change in taste or smell	1.03	(0.63, 1.66)	0.025	0.1485	8.66E-01	1.00E+00
Chills	2.22	(1.35, 3.66)	0.7975	0.1542	2.31E-07	9.70E-06
Cough producing phlegm	1.69	(1.05, 2.70)	0.5233	0.1452	3.14E-04	1.32E-02
Diarrhea	2.74	(1.71, 4.39)	1.0077	0.1457	4.58E-12	1.92E-10
Dry cough	2.73	(1.62, 4.59)	1.0041	0.1601	3.60E-10	1.51E-08
Feeling tired or fatigue	2.86	(1.10, 7.40)	1.05	0.2938	3.51E-04	1.48E-02
Fever	3.34	(1.91, 5.85)	1.2074	0.1726	2.65E-12	1.11E-10
Headache	1.18	(0.72, 1.95)	0.1678	0.1537	2.75E-01	1.00E+00
Nasal congestion	1.12	(0.70, 1.78)	0.1106	0.1435	4.41E-01	1.00E+00
Nausea or vomiting	2.72	(1.65, 4.49)	0.9997	0.1547	1.03E-10	4.31E-09
Runny nose	1.19	(0.72, 1.95)	0.1704	0.153	2.65E-01	1.00E+00
Shortness of breath	12.87	(6.18, 26.81)	2.5549	0.2265	1.62E-29	6.79E-28
Sore throat	1.65	(1.01, 2.68)	0.4991	0.1503	9.01E-04	3.79E-02

Adjusted odds ratios for progression of COVID-19 infection to a critical, life-threatening illness were calculated among those reporting a positive COVID-19 test result. The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods). Here, odds ratios were adjusted for age, sex, comorbitidies (Y/N if any), and obesity (Y/N if BMI > 30, Methods).

Supplementary Table 17. Unadjusted risk factor odds ratios for COVID-19 susceptibility (training dataset)

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	1.6	(1.21, 2.11)	0.4693	0.0857	4.42E-08	1.86E-06
Ages 30-49	1.11	(0.92, 1.34)	0.105	0.0584	7.22E-02	1.00E+00
Ages 50-64	1		0		nan	nan
Ages 65+	0.49	(0.38, 0.63)	-0.7051	0.077	0.00E+00	0.00E+00
GENETIC ANCESTRY						
Admixed African-European	1.24	(0.85, 1.81)	0.2158	0.1168	6.47E-02	1.00E+00
European	1		0		nan	nan
Admixed Amerindian	1.59	(1.22, 2.07)	0.462	0.0814	1.36E-08	5.73E-07
Other	1.16	(0.94, 1.44)	0.1516	0.0665	2.27E-02	9.52E-01
EXPOSURE						
Any	9.49	(7.65, 11.77)	2.2503	0.0665	4.79E-251	2.01E-249
Biological relative tested positive	5.74	(4.66, 7.07)	1.7467	0.0644	4.71E-162	1.98E-160
Directly exposed to someone who tested positive	7.63	(6.33, 9.19)	2.0317	0.0576	4.44E-272	1.87E-270
Healthcare worker directly exposed	1.56	(1.29, 1.87)	0.4417	0.0576	1.78E-14	7.47E-13
Household member tested positive	24.28	(19.62, 30.03)	3.1896	0.0657	0.00E+00	0.00E+00
PRE-EXISTING CONDITION						
Asthma	0.81	(0.65, 1.00)	-0.2166	0.0677	1.37E-03	5.75E-02
COPD (Chronic Obstructive Pulmonary Disease)	0.54	(0.31, 0.93)	-0.6217	0.1684	2.22E-04	9.32E-03
Cancer treated in the past year	0.57	(0.32, 1.00)	-0.564	0.1731	1.12E-03	4.71E-02
Cardiovascular disease	0.74	(0.51, 1.06)	-0.3014	0.1122	7.26E-03	3.05E-01
Chronic kidney disease	0.55	(0.28, 1.10)	-0.5938	0.2139	5.49E-03	2.31E-01
Diabetes	0.9	(0.69, 1.17)	-0.105	0.0816	1.98E-01	1.00E+00
Hypertension	0.76	(0.62, 0.93)	-0.2728	0.061	7.64E-06	3.21E-04
Other	0.93	(0.66, 1.31)	-0.0726	0.1049	4.89E-01	1.00E+00
Other autoimmune disease	0.8	(0.61, 1.04)	-0.2241	0.081	5.65E-03	2.37E-01
Other immunodeficiency disorder	0.77	(0.42, 1.40)	-0.2669	0.1854	1.50E-01	1.00E+00
Other lung condition	0.64	(0.39, 1.03)	-0.4524	0.1502	2.59E-03	1.09E-01

Any	0.67	(0.57, 0.79)	-0.3983	0.0498	1.33E-15	5.60E-14
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.02	(0.83, 1.25)	0.0212	0.0628	7.35E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.15	(0.94, 1.41)	0.1376	0.0626	2.81E-02	1.00E+00
obesity III (BMI >= 40)	1.13	(0.85, 1.50)	0.12	0.0874	1.70E-01	1.00E+00
Not obese	1		0		nan	nan
GENETIC SEX						
Female	1		0		nan	nan
Male	1.16	(0.98, 1.37)	0.1459	0.0525	5.43E-03	2.28E-01
SYMPTOMS						
Abdominal pain	0.97	(0.64, 1.48)	-0.0303	0.1303	8.16E-01	1.00E+00
Body aches	1.56	(1.09, 2.23)	0.4461	0.1104	5.34E-05	2.24E-03
Change in taste or smell	7.02	(4.67, 10.56)	1.9493	0.1257	2.96E-54	1.24E-52
Chills	1.38	(0.97, 1.96)	0.3211	0.1085	3.08E-03	1.29E-01
Cough producing phlegm	0.93	(0.64, 1.37)	-0.0685	0.1178	5.61E-01	1.00E+00
Diarrhea	1.18	(0.81, 1.72)	0.1672	0.1158	1.49E-01	1.00E+00
Dry cough	1.29	(0.91, 1.84)	0.2578	0.1082	1.72E-02	7.21E-01
Feeling tired or fatigue	1.54	(0.99, 2.42)	0.4341	0.1381	1.67E-03	7.03E-02
Fever	1.54	(1.08, 2.19)	0.4295	0.1088	7.84E-05	3.29E-03
Headache	1.39	(0.97, 2.00)	0.33	0.1118	3.17E-03	1.33E-01
Nasal congestion	0.85	(0.60, 1.21)	-0.1632	0.1081	1.31E-01	1.00E+00
Nausea or vomiting	0.82	(0.53, 1.26)	-0.1979	0.1327	1.36E-01	1.00E+00
Runny nose	0.59	(0.41, 0.86)	-0.5246	0.1137	3.92E-06	1.65E-04
Shortness of breath	1.25	(0.87, 1.79)	0.2219	0.1106	4.48E-02	1.00E+00
Sore throat	0.48	(0.34, 0.69)	-0.7286	0.1117	6.84E-11	2.87E-09

Unadjusted odds ratios for a positive COVID-19 test were calculated among survey participants reporting a test result (positive or negative). The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods).

714 **Supplementary Table 18. Unadjusted risk factor odds ratios for COVID-19 hospitalization**
715 **(training dataset)**

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RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	0.53	(0.20, 1.37)	-0.6395	0.2951	3.02E-02	1.00E+00
Ages 30-49	0.5	(0.27, 0.92)	-0.6907	0.1879	2.37E-04	9.95E-03
Ages 50-64	1		0		nan	nan
Ages 65+	1.64	(0.87, 3.08)	0.4956	0.1943	1.07E-02	4.51E-01
GENETIC ANCESTRY						
Admixed African-European	1.19	(0.43, 3.28)	0.176	0.3121	5.73E-01	1.00E+00
European	1		0		nan	nan
Admixed Amerindian	0.77	(0.32, 1.86)	-0.2551	0.2703	3.45E-01	1.00E+00
Other	0.69	(0.34, 1.39)	-0.3752	0.2169	8.37E-02	1.00E+00
EXPOSURE						
Any	0.69	(0.34, 1.39)	-0.3732	0.2174	8.61E-02	1.00E+00
Biological relative tested positive	1.06	(0.60, 1.88)	0.0572	0.1772	7.47E-01	1.00E+00
Directly exposed to someone who tested positive	0.54	(0.29, 0.98)	-0.6207	0.1867	8.86E-04	3.72E-02
Healthcare worker directly exposed	0.57	(0.29, 1.10)	-0.5698	0.2042	5.26E-03	2.21E-01
Household member tested positive	0.88	(0.53, 1.45)	-0.1332	0.1551	3.90E-01	1.00E+00
HEALTH CONDITIONS						
Asthma	1.17	(0.62, 2.19)	0.1555	0.1944	4.24E-01	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	2.95	(0.82, 10.67)	1.083	0.3962	6.27E-03	2.63E-01
Cancer treated in the past year	3.21	(0.88, 11.78)	1.1677	0.4006	3.56E-03	1.49E-01
Cardiovascular disease	2.73	(1.18, 6.28)	1.0036	0.2573	9.62E-05	4.04E-03
Chronic kidney disease	10.82	(2.86, 40.90)	2.3812	0.4103	6.49E-09	2.73E-07
Diabetes	3.21	(1.70, 6.06)	1.1676	0.1957	2.44E-09	1.02E-07
Hypertension	1.68	(0.98, 2.88)	0.5172	0.1664	1.88E-03	7.91E-02
Other	1.63	(0.74, 3.63)	0.4906	0.2463	4.64E-02	1.00E+00
Other autoimmune disease	1.21	(0.58, 2.54)	0.1914	0.2288	4.03E-01	1.00E+00
Other immunodeficiency disorder	0.77	(0.11, 5.53)	-0.2655	0.6094	6.63E-01	1.00E+00

Other lung condition	1.8	(0.50, 6.55)	0.5883	0.3983	1.40E-01	1.00E+00
Any	2.36	(1.41, 3.93)	0.8574	0.1575	5.26E-08	2.21E-06
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.32	(0.74, 2.34)	0.2765	0.1771	1.19E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.08	(0.56, 2.06)	0.0753	0.2001	7.07E-01	1.00E+00
obesity III (BMI >= 40)	1.42	(0.62, 3.26)	0.3505	0.2566	1.72E-01	1.00E+00
Not obese	1		0		nan	nan
GENETIC SEX						
Female	1		0		nan	nan
Male	1.29	(0.79, 2.12)	0.2584	0.1525	9.02E-02	1.00E+00
SYMPTOMS						
Abdominal pain	1.79	(1.04, 3.10)	0.5841	0.1686	5.33E-04	2.24E-02
Body aches	1.6	(0.90, 2.83)	0.4695	0.1765	7.80E-03	3.28E-01
Change in taste or smell	0.83	(0.50, 1.38)	-0.189	0.1582	2.32E-01	1.00E+00
Chills	2.18	(1.29, 3.71)	0.7814	0.1632	1.68E-06	7.07E-05
Cough producing phlegm	1.51	(0.90, 2.53)	0.4096	0.1596	1.03E-02	4.31E-01
Diarrhea	2.04	(1.24, 3.36)	0.7114	0.154	3.87E-06	1.62E-04
Dry cough	2.5	(1.47, 4.28)	0.9179	0.1653	2.80E-08	1.18E-06
Feeling tired or fatigue	4.47	(1.35, 14.73)	1.4965	0.3681	4.79E-05	2.01E-03
Fever	3.06	(1.72, 5.44)	1.1178	0.178	3.36E-10	1.41E-08
Headache	0.87	(0.52, 1.47)	-0.1351	0.16	3.99E-01	1.00E+00
Nasal congestion	0.73	(0.44, 1.23)	-0.3139	0.1595	4.90E-02	1.00E+00
Nausea or vomiting	2.48	(1.45, 4.23)	0.9068	0.1653	4.13E-08	1.74E-06
Runny nose	0.87	(0.49, 1.55)	-0.1355	0.1777	4.46E-01	1.00E+00
Shortness of breath	6.4	(3.49, 11.73)	1.8558	0.187	3.34E-23	1.40E-21
Sore throat	1.03	(0.59, 1.80)	0.0332	0.1717	8.47E-01	1.00E+00

Unadjusted odds ratios for hospitalization due to COVID-19 infection were calculated among those reporting a positive COVID-19 test result. The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods).

724 **Supplementary Table 19. Unadjusted risk factor odds ratios for progression of COVID-19**
725 **to a critical case (training dataset)**

726

RISK FACTOR	ODDS RATIO (OR)	OR 95% CI (BONFERRONI)	logOR	logOR S.E.	P-VALUE (NOMINAL)	P-VALUE (BONFERRONI)
AGE						
Ages 18-29	0.48	(0.12, 1.84)	-0.7444	0.4175	7.46E-02	1.00E+00
Ages 30-49	0.61	(0.28, 1.33)	-0.4935	0.2408	4.04E-02	1.00E+00
Ages 50-64	1		0		nan	nan
Ages 65+	1.32	(0.56, 3.12)	0.2779	0.2651	2.95E-01	1.00E+00
GENETIC ANCESTRY						
Admixed African-European	2.2	(0.72, 6.73)	0.7892	0.3445	2.20E-02	9.24E-01
European	1		0		nan	nan
Admixed Amerindian	1.08	(0.36, 3.21)	0.0779	0.3354	8.16E-01	1.00E+00
Other	0.84	(0.34, 2.13)	-0.1692	0.2852	5.53E-01	1.00E+00
EXPOSURE						
Any	0.67	(0.26, 1.72)	-0.3951	0.2884	1.71E-01	1.00E+00
Biological relative tested positive	1.18	(0.56, 2.50)	0.1677	0.2304	4.67E-01	1.00E+00
Directly exposed to someone who tested positive	0.46	(0.20, 1.03)	-0.7835	0.2502	1.74E-03	7.31E-02
Healthcare worker directly exposed	0.61	(0.25, 1.47)	-0.4938	0.2711	6.85E-02	1.00E+00
Household member tested positive	0.99	(0.51, 1.93)	-0.0064	0.2055	9.75E-01	1.00E+00
PRE-EXISTING CONDITION						
Asthma	1.04	(0.44, 2.46)	0.0353	0.2669	8.95E-01	1.00E+00
COPD (Chronic Obstructive Pulmonary Disease)	4.34	(1.06, 17.88)	1.4689	0.4366	7.66E-04	3.22E-02
Cancer treated in the past year	1.66	(0.23, 12.21)	0.5094	0.6149	4.07E-01	1.00E+00
Cardiovascular disease	2.88	(1.03, 8.08)	1.0584	0.318	8.74E-04	3.67E-02
Chronic kidney disease	13.83	(3.59, 53.34)	2.6267	0.4165	2.85E-10	1.20E-08
Diabetes	3.53	(1.61, 7.75)	1.2624	0.2422	1.86E-07	7.82E-06
Hypertension	2.16	(1.09, 4.29)	0.7721	0.2113	2.59E-04	1.09E-02
Other	1.64	(0.58, 4.63)	0.4926	0.3206	1.24E-01	1.00E+00
Other autoimmune disease	1.28	(0.49, 3.36)	0.2478	0.2976	4.05E-01	1.00E+00
Other immunodeficiency disorder	2.16	(0.37, 12.54)	0.7723	0.542	1.54E-01	1.00E+00

Other lung condition	3.74	(1.01, 13.88)	1.3195	0.4045	1.10E-03	4.64E-02
Any	3.13	(1.52, 6.45)	1.1406	0.2233	3.25E-07	1.37E-05
OBESITY						
obesity I (BMI >= 30 and BMI < 35)	1.24	(0.57, 2.68)	0.2116	0.2385	3.75E-01	1.00E+00
obesity II (BMI >= 35 and BMI < 40)	1.12	(0.48, 2.62)	0.1104	0.2632	6.75E-01	1.00E+00
obesity III (BMI >= 40)	1.5	(0.51, 4.38)	0.4053	0.3305	2.20E-01	1.00E+00
Not obese	1		0		nan	nan
GENETIC SEX						
Female	1		0		nan	nan
Male	1.53	(0.80, 2.94)	0.4266	0.2013	3.41E-02	1.00E+00
SYMPTOMS						
Abdominal pain	2.02	(1.01, 4.06)	0.7042	0.2147	1.04E-03	4.37E-02
Body aches	2.16	(0.95, 4.93)	0.7723	0.2541	2.37E-03	9.95E-02
Change in taste or smell	0.73	(0.37, 1.41)	-0.3191	0.2051	1.20E-01	1.00E+00
Chills	2.32	(1.14, 4.72)	0.8403	0.2196	1.30E-04	5.44E-03
Cough producing phlegm	1.89	(0.97, 3.66)	0.6342	0.2046	1.94E-03	8.13E-02
Diarrhea	2.33	(1.21, 4.48)	0.844	0.2021	2.96E-05	1.24E-03
Dry cough	2.69	(1.30, 5.56)	0.9909	0.2238	9.53E-06	4.00E-04
Feeling tired or fatigue	6.27	(0.93, 42.41)	1.8352	0.59	1.87E-03	7.84E-02
Fever	3.33	(1.50, 7.36)	1.2022	0.2449	9.18E-07	3.85E-05
Headache	0.86	(0.44, 1.70)	-0.1487	0.2098	4.78E-01	1.00E+00
Nasal congestion	0.92	(0.48, 1.80)	-0.0791	0.2053	7.00E-01	1.00E+00
Nausea or vomiting	2.43	(1.22, 4.84)	0.8874	0.2129	3.07E-05	1.29E-03
Runny nose	0.95	(0.45, 2.01)	-0.0495	0.2303	8.30E-01	1.00E+00
Shortness of breath	10.57	(3.99, 28.02)	2.3584	0.3007	4.35E-15	1.83E-13
Sore throat	1.27	(0.63, 2.57)	0.2369	0.2177	2.76E-01	1.00E+00

Unadjusted odds ratios for progression of COVID-19 infection to a critical, life-threatening illness were calculated among those reporting a positive COVID-19 test result. The following groups served as reference populations for the odds ratio calculations: European genetic ancestry (Genetic Ancestry), Ages 50-64 (Age), Female (Genetic Sex), and Not Obese (BMI < 30, Obesity). Note that symptoms odds ratios were calculated in a binary fashion among symptomatic customers only (Methods).

735 **Supplementary Table 20. Summary of risk factors and performances of different models**
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Model	Risk Factors in Final Model	Holdout AUC (95% CI)
Susceptibility– symptoms excluded (Dem + Exp)	sex, aged 18-29 (Y/N), aged 30-49 (Y/N), aged 50-64 (Y/N), aged 65+ (Y/N), Healthcare worker directly exposed, Household member tested positive, Household positive case count, Biological relative tested positive, Directly exposed to someone who tested positive	0.84 (0.82, 0.86)
Susceptibility– symptoms included (Dem + Exp + Symp)	sex, Fever, Runny nose, Sore throat, Feeling tired or fatigue, Change in taste or smell, aged 18-29 (Y/N), aged 30-49 (Y/N), aged 50-64 (Y/N), aged 65+ (Y/N), Healthcare worker directly exposed, Household member tested positive, Household positive case count, Biological relative tested positive, Directly exposed to someone who tested positive	0.94 (0.92, 0.96)
Susceptibility– symptoms excluded, L1-penalized model across larger set of risk factors	aged 18-29 (Y/N), aged 30-49 (Y/N), aged 65+ (Y/N), Biological relative tested positive, Directly exposed to someone who tested positive, Hypertension, Healthcare worker directly exposed, Household positive case count, Household member tested positive, Health condition (Y/N if any)	0.86 (0.85, 0.87)
Susceptibility– symptoms included, L1-penalized model across larger set of risk factors	aged 18-29 (Y/N), aged 30-49 (Y/N), aged 65+ (Y/N), Biological relative tested positive, Directly exposed to someone who tested positive, Hypertension, Healthcare worker directly exposed, Household positive case count, Household member tested positive, Health condition (Y/N if any), Abdominal pain, Body aches, Change in taste or smell, Chills, Cough producing phlegm, Diarrhea, Dry cough, Feeling tired or fatigue, Fever, Headache, Nasal congestion, Nausea or vomiting, Runny nose, Shortness of breath, Sore throat	0.90 (0.86, 0.94)
Susceptibility– literature-based "minimal" model (HWF Exp + Symp)	Change in taste or smell, Household member tested positive, Directly exposed to someone who tested positive	0.90 (0.88, 0.93)
Susceptibility– literature-based "symptoms-only" model (HWF Symp)	Fever, Shortness of breath, Dry cough, Sore throat,Chills, Body aches, Change in taste or smell	0.87 (0.84, 0.90)
Severity– hospitalization	sex, Fever, Shortness of breath, Dry cough, Feeling tired or fatigue, Diarrhea, Obesity III (BMI >= 40), aged 18-29 (Y/N), aged 30-49 (Y/N), aged 50-64 (Y/N), aged 65+ (Y/N), Health condition (Y/N if any)	0.87 (0.84, 0.90)
Severity– hospitalization, L1-penalized model across larger set of risk factors	aged 30-49 (Y/N), aged 50-64 (Y/N), aged 65+ (Y/N), COPD (Chronic Obstructive Pulmonary Disease), Cancer (treated in the past year), Cardiovascular disease, Chronic kidney disease, Diabetes, Hypertension, Other, Health condition (Y/N if any), Abdominal pain, Chills, Cough producing phlegm, Diarrhea, Dry cough, Feeling tired or fatigue, Fever, Nausea or vomiting, Shortness of breath	0.87 (0.86, 0.88)
Severity– critical case	sex, Fever, Shortness of breath, Dry cough, Feeling tired or fatigue, Diarrhea, Obesity III (BMI >= 40), aged 18-29 (Y/N), aged 30-49 (Y/N), aged 50-64 (Y/N), aged 65+ (Y/N), Health condition (Y/N if any)	0.90 (0.87, 0.93)
Severity– critical case, L1-penalized model across larger set of risk factors	aged 30-49 (Y/N), aged 65+ (Y/N), COPD (Chronic Obstructive Pulmonary Disease), Cardiovascular disease, Chronic kidney disease, Diabetes, Hypertension, Other lung condition, Health condition (Y/N if any), Seasonal flu, sex, Abdominal pain, Body aches, Chills, Cough producing phlegm, Diarrhea, Dry cough, Feeling tired or fatigue, Fever, Nausea or vomiting, Shortness of breath	0.89 (0.87, 0.91)

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739 Risk factors for models were selected based on literature as well as nominally significant odds
740 ratios within the training dataset (Methods). 95% confidence intervals for the area under the
741 curve (AUC) on the holdout dataset were estimated via bootstrapping (Methods).
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Supplementary Table 21. Stratified holdout performance assessment for a COVID-19 susceptibility model built from age, sex, and exposures (Dem + Exp)

cohort	N	ncase	ncontrol	AUC	Sensitivity	Specificity
Admixed African-European Genetic Ancestry	228	38	190	0.88 (0.82, 0.94)	0.89 (0.80, 0.99)	0.65 (0.59, 0.72)
All	4834	632	4202	0.84 (0.82, 0.86)	0.75 (0.72, 0.79)	0.76 (0.75, 0.78)
European Genetic Ancestry	3372	408	2964	0.84 (0.82, 0.87)	0.74 (0.70, 0.78)	0.79 (0.77, 0.80)
Admixed Amerindian Genetic Ancestry	410	73	337	0.80 (0.74, 0.86)	0.74 (0.64, 0.84)	0.71 (0.66, 0.75)
Other Genetic Ancestry	824	113	711	0.83 (0.78, 0.87)	0.77 (0.69, 0.85)	0.71 (0.68, 0.75)
Ages 18-29	340	74	266	0.83 (0.77, 0.89)	0.81 (0.72, 0.90)	0.65 (0.59, 0.71)
Ages 30-49	1744	270	1474	0.80 (0.77, 0.83)	0.82 (0.77, 0.86)	0.59 (0.56, 0.61)
Ages 50-65	1515	200	1315	0.85 (0.82, 0.88)	0.73 (0.67, 0.79)	0.81 (0.79, 0.83)
Ages 65+	1235	88	1147	0.81 (0.75, 0.87)	0.57 (0.47, 0.67)	0.96 (0.95, 0.97)
Female	3354	409	2945	0.83 (0.81, 0.85)	0.73 (0.68, 0.77)	0.77 (0.75, 0.79)
Male	1480	223	1257	0.85 (0.82, 0.88)	0.81 (0.76, 0.86)	0.75 (0.73, 0.77)

Case/control status is defined based on a self-reported COVID-19 positive test result. The Dem + Exp model includes questions about exposures, age, and sex (Supplementary Table 20). Metric performance columns reflect mean and nominal 95% confidence intervals for each metric on an internal, independent holdout dataset (Methods). Cohort-level receiver operator characteristic (ROC) curves were constructed from predicted class probabilities of models trained on the entire training dataset (Methods).

Supplementary Table 22. Stratified holdout performance assessment for a COVID-19 susceptibility model built from age, sex, exposures, and symptoms (Dem + Exp + Symp)

cohort	N	ncase	ncontrol	AUC	Sensitivity	Specificity
Admixed African-European Genetic Ancestry	96	12	84	0.96 (0.88, 1.00)	0.91 (0.75, 1.00)	0.92 (0.86, 0.98)
All	2047	229	1818	0.94 (0.92, 0.96)	0.85 (0.80, 0.89)	0.91 (0.90, 0.93)
European Genetic Ancestry	1457	146	1311	0.93 (0.90, 0.96)	0.83 (0.77, 0.90)	0.91 (0.90, 0.93)
Admixed Amerindian Genetic Ancestry	155	23	132	0.98 (0.95, 1.00)	0.96 (0.87, 1.00)	0.89 (0.84, 0.95)
Other Genetic Ancestry	339	48	291	0.94 (0.90, 0.99)	0.81 (0.70, 0.92)	0.93 (0.90, 0.96)
Ages 18-29	132	29	103	0.98 (0.95, 1.00)	0.93 (0.84, 1.00)	0.92 (0.87, 0.97)
Ages 30-49	582	77	505	0.96 (0.95, 0.98)	0.89 (0.82, 0.96)	0.88 (0.85, 0.91)
Ages 50-65	616	83	533	0.93 (0.90, 0.97)	0.84 (0.76, 0.92)	0.91 (0.88, 0.93)
Ages 65+	717	40	677	0.89 (0.83, 0.96)	0.72 (0.58, 0.86)	0.95 (0.93, 0.97)
Female	1380	139	1241	0.94 (0.91, 0.97)	0.86 (0.80, 0.92)	0.91 (0.89, 0.92)
Male	667	90	577	0.94 (0.90, 0.97)	0.83 (0.76, 0.91)	0.93 (0.91, 0.96)

Case/control status is defined based on self-reported COVID-19 positive test result. The Dem + Exp + Symp model includes questions about exposures, age, sex, and five symptom questions (Supplementary Table 20). Metric performance columns reflect mean and nominal 95% confidence intervals for each metric on an internal, independent holdout dataset (Methods). Cohort-level receiver operator characteristic (ROC) curves were constructed from predicted class probabilities of models trained on the entire training dataset (Methods).

Supplementary Table 23. Stratified holdout performance assessment for a literature-based COVID-19 susceptibility model based on two exposures and one symptom (HWF Exp + Symp)

cohort	N	ncase	ncontrol	AUC	Sensitivity	Specificity
Admixed African-European Genetic Ancestry	96	12	84	0.94 (0.84, 1.00)	0.92 (0.76, 1.00)	0.94 (0.89, 0.99)
All	2047	229	1818	0.90 (0.88, 0.93)	0.78 (0.73, 0.83)	0.94 (0.93, 0.95)
European Genetic Ancestry	1457	146	1311	0.89 (0.86, 0.92)	0.75 (0.68, 0.82)	0.94 (0.93, 0.95)
Admixed Amerindian Genetic Ancestry	155	23	132	0.94 (0.88, 1.00)	0.87 (0.73, 1.00)	0.92 (0.87, 0.97)
Other Genetic Ancestry	339	48	291	0.92 (0.87, 0.97)	0.79 (0.68, 0.90)	0.96 (0.94, 0.98)
Ages 18-29	132	29	103	0.92 (0.85, 0.99)	0.79 (0.65, 0.94)	0.96 (0.92, 1.00)
Ages 30-49	582	77	505	0.91 (0.86, 0.95)	0.82 (0.73, 0.91)	0.92 (0.90, 0.95)
Ages 50-65	616	83	533	0.91 (0.87, 0.95)	0.81 (0.73, 0.89)	0.93 (0.91, 0.95)
Ages 65+	717	40	677	0.85 (0.77, 0.92)	0.65 (0.50, 0.80)	0.96 (0.95, 0.98)
Female	1380	139	1241	0.91 (0.88, 0.94)	0.81 (0.75, 0.88)	0.94 (0.92, 0.95)
Male	667	90	577	0.89 (0.85, 0.94)	0.73 (0.64, 0.83)	0.95 (0.94, 0.97)

Case/control status is defined based on self-reported COVID-19 positive test result. The literature-based HWF Exp + Symp model contains two exposure questions and a question about one symptom (change in taste or smell, Supplementary Table 20).[18] Metric performance columns reflect mean and nominal 95% confidence intervals for each metric on an internal, independent holdout dataset (Methods). Cohort-level receiver operator characteristic (ROC) curves were constructed from predicted class probabilities of models trained on the entire training dataset (Methods).

Supplementary Table 24. Stratified holdout performance assessment for a literature-based COVID-19 susceptibility model based on seven symptoms (HWF Symp)

cohort	N	ncase	ncontrol	AUC	Sensitivity	Specificity
Admixed African-European Genetic Ancestry	96	12	84	0.90 (0.77, 1.00)	0.84 (0.62, 1.00)	0.92 (0.86, 0.98)
All	2047	229	1818	0.87 (0.84, 0.90)	0.75 (0.69, 0.80)	0.91 (0.90, 0.93)
European Genetic Ancestry	1457	146	1311	0.87 (0.83, 0.91)	0.75 (0.68, 0.82)	0.91 (0.89, 0.93)
Admixed Amerindian Genetic Ancestry	155	23	132	0.92 (0.85, 0.99)	0.87 (0.73, 1.00)	0.93 (0.89, 0.97)
Other Genetic Ancestry	339	48	291	0.83 (0.76, 0.91)	0.67 (0.53, 0.80)	0.92 (0.89, 0.95)
Ages 18-29	132	29	103	0.85 (0.75, 0.96)	0.79 (0.64, 0.95)	0.94 (0.90, 0.99)
Ages 30-49	582	77	505	0.89 (0.85, 0.93)	0.75 (0.66, 0.85)	0.88 (0.85, 0.91)
Ages 50-65	616	83	533	0.86 (0.80, 0.91)	0.75 (0.65, 0.84)	0.89 (0.87, 0.92)
Ages 65+	717	40	677	0.84 (0.76, 0.92)	0.70 (0.55, 0.85)	0.95 (0.93, 0.96)
Female	1380	139	1241	0.87 (0.83, 0.91)	0.76 (0.69, 0.83)	0.90 (0.88, 0.92)
Male	667	90	577	0.87 (0.83, 0.92)	0.73 (0.63, 0.82)	0.94 (0.92, 0.96)

Case/control status is defined based on self-reported COVID-19 positive test result. The literature-based HWF Symp model contains 7 symptoms most commonly associated with COVID-19 (Supplementary Table 20).[18] Metric performance columns reflect mean and nominal 95% confidence intervals for each metric on an internal, independent holdout dataset (Methods). Cohort-level receiver operator characteristic (ROC) curves were constructed from predicted class probabilities of models trained on the entire training dataset (Methods).

Supplementary Table 25. Comparison between train and holdout performances for different risk models

Model	Train AUC (95% CI)	Holdout AUC (95% CI)
Susceptibility– no symptoms (Dem + Exp)	0.83 (0.81, 0.85)	0.84 (0.82, 0.84)
Susceptibility– with symptoms (Dem + Exp + Symp)	0.95 (0.93, 0.97)	0.94 (0.92, 0.96)
Susceptibility– literature-based "minimal" model (HWF Exp + Symp)	0.90 (0.88, 0.92)	0.90 (0.88, 0.93)
Susceptibility– literature-based "symptoms-only" model (HWF Symp)	0.87 (0.84, 0.90)	0.87 (0.84, 0.90)
Severity– hospitalization	0.85 (0.82, 0.88)	0.87 (0.84, 0.90)
Severity– critical case of COVID-19	0.90 (0.87, 0.93)	0.90 (0.87, 0.93)

Columns reflect mean and nominal 95% confidence intervals for the area under the curve (AUC) of trained models on either the training or holdout dataset. Confidence intervals were estimated via bootstrapping (Methods).

Supplementary Table 26. Stratified holdout performance assessment for models to predict hospitalization amongst COVID-19 positive cases

cohort	N	ncase	ncontrol	Auc	Sensitivity	Specificity
Admixed African-European Genetic Ancestry	110	20	90	0.81 (0.72, 0.90)	0.85 (0.68, 1.00)	0.71 (0.62, 0.80)
All	1793	191	1602	0.87 (0.84, 0.90)	0.83 (0.78, 0.88)	0.75 (0.73, 0.77)
European Genetic Ancestry	1133	120	1013	0.87 (0.84, 0.90)	0.82 (0.76, 0.89)	0.74 (0.72, 0.77)
Admixed Amerindian Genetic Ancestry	219	16	203	0.94 (0.90, 0.98)	0.93 (0.81, 1.00)	0.79 (0.74, 0.85)
Other Genetic Ancestry	331	35	296	0.85 (0.77, 0.93)	0.80 (0.67, 0.94)	0.75 (0.70, 0.80)
Ages 18-29	201	7	194	0.95 (0.91, 0.99)	0.85 (0.57, 1.00)	0.90 (0.85, 0.94)
Ages 30-49	705	49	656	0.87 (0.82, 0.93)	0.76 (0.63, 0.88)	0.85 (0.82, 0.88)
Ages 50-65	616	78	538	0.86 (0.81, 0.90)	0.86 (0.78, 0.94)	0.65 (0.61, 0.69)
Ages 65+	271	57	214	0.78 (0.72, 0.85)	0.86 (0.77, 0.95)	0.53 (0.47, 0.60)
Female	1166	118	1048	0.87 (0.83, 0.90)	0.80 (0.72, 0.87)	0.77 (0.74, 0.79)
Male	627	73	554	0.87 (0.83, 0.91)	0.89 (0.82, 0.96)	0.71 (0.67, 0.75)

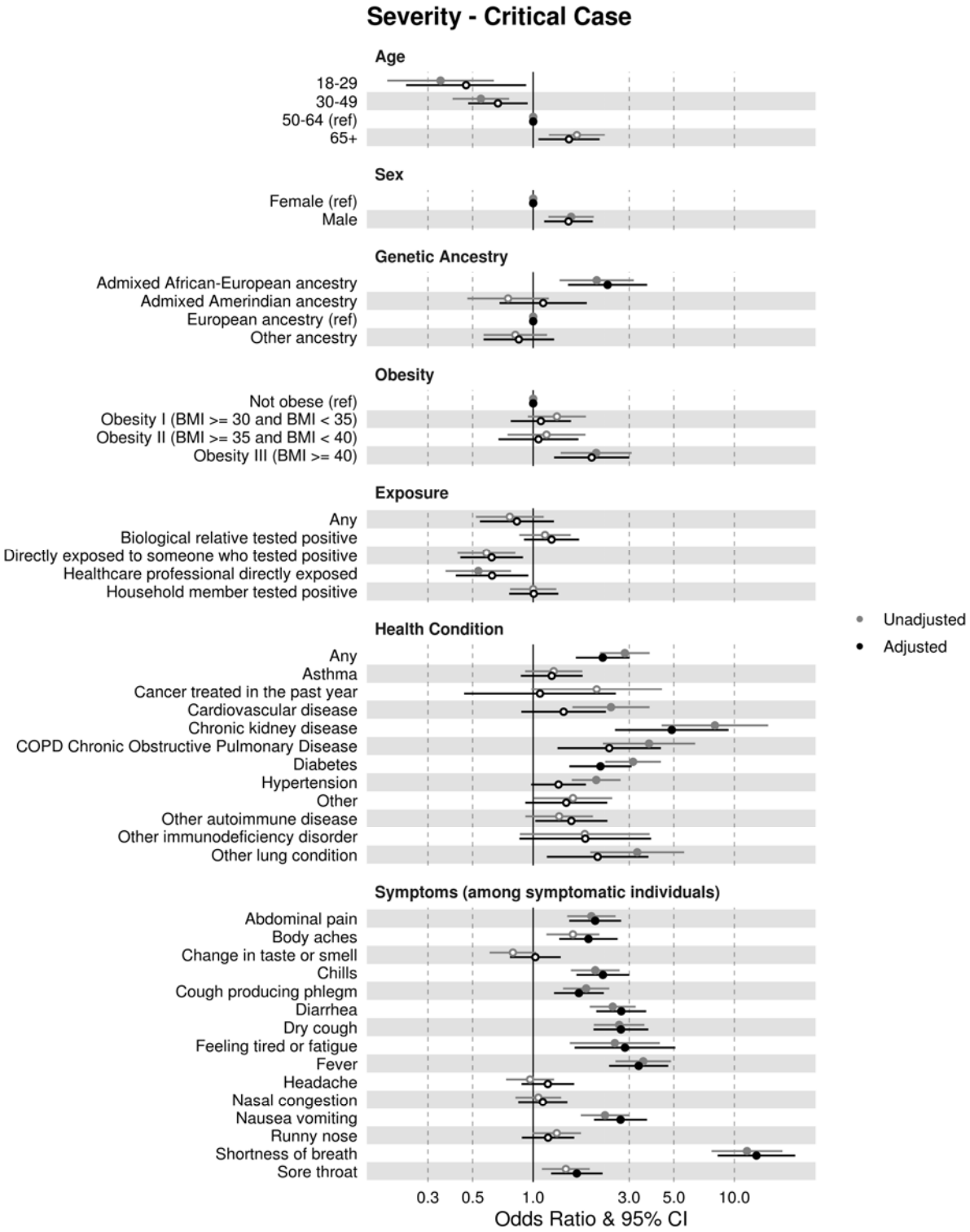
Case/control status is defined based on self-reported hospitalization due to COVID-19-related illness (Methods). Metric performance columns reflect mean and nominal 95% confidence intervals for each metric on an internal, independent holdout dataset (Methods). Cohort-level receiver operator characteristic (ROC) curves were constructed from predicted class probabilities of models trained on the entire survey cohort (Methods).

Supplementary Table 27. Stratified holdout performance assessment for models to predict critical COVID-19 cases amongst all COVID-19 positive cases

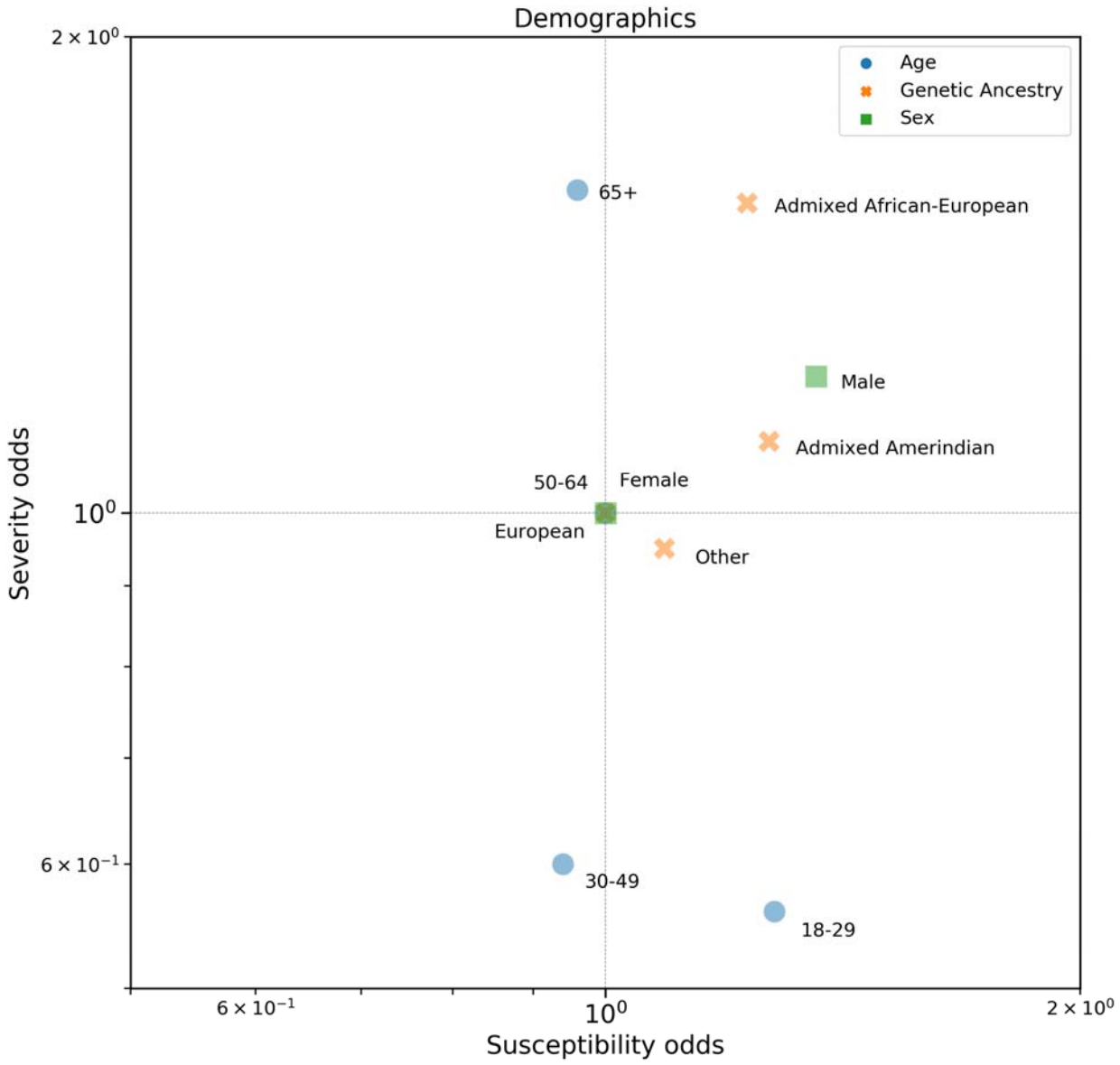
cohort	N	ncase	ncontrol	AUC	Sensitivity	Specificity
Admixed African-European Genetic Ancestry	110	15	95	0.87 (0.78, 0.97)	0.93 (0.80, 1.00)	0.75 (0.66, 0.83)
All	1793	105	1688	0.90 (0.87, 0.93)	0.93 (0.87, 0.98)	0.79 (0.77, 0.81)
European Genetic Ancestry	1133	70	1063	0.90 (0.86, 0.93)	0.90 (0.83, 0.97)	0.79 (0.76, 0.81)
Admixed Amerindian Genetic Ancestry	219	7	212	0.92 (0.88, 0.96)	1.00 (0.60, 1.00)	0.83 (0.78, 0.88)
Other Genetic Ancestry	331	13	318	0.92 (0.87, 0.97)	1.00 (0.73, 1.00)	0.77 (0.73, 0.82)
Ages 18-29	201	2	199	0.96 (0.92, 0.99)	1.00 (0.29, 1.00)	0.92 (0.88, 0.96)
Ages 30-49	705	24	681	0.94 (0.92, 0.96)	1.00 (0.84 1.00)	0.84 (0.81, 0.87)
Ages 50-65	616	43	573	0.87 (0.82, 0.93)	0.91 (0.82, 0.99)	0.71 (0.68, 0.75)
Ages 65+	271	36	235	0.84 (0.78, 0.91)	0.89 (0.78, 0.99)	0.71 (0.66, 0.77)
Female	1166	60	1106	0.90 (0.86, 0.94)	0.93 (0.87, 1.00)	0.80 (0.77, 0.83)
Male	627	45	582	0.89 (0.85, 0.93)	0.91 (0.83, 0.99)	0.77 (0.73, 0.80)

Case/control status is defined based on self-reported critical case progression among all COVID-19 cases. Here, a critical case is defined based on self-reported ICU admittance, respiratory failure, organ failure, or septic shock resulting from COVID-19-related illness (Methods). Metric performance columns reflect mean and nominal 95% confidence intervals for each metric on an internal, independent holdout dataset (Methods). Cohort-level receiver operator characteristic (ROC) curves were constructed from predicted class probabilities of models trained on the entire survey cohort (Methods).

Supplementary Figures



Supplementary Figure 1. Severity (critical case) odds ratios (ORs) and 95% confidence intervals (CIs) estimated from simple ("Unadjusted models," grey) and multiple ("Adjusted models," black) logistic regression with adjustment for other risk factors. Open circles indicate not significant (p-value > 0.05) after accounting for multiple hypothesis tests using Bonferroni correction. Age, sex, genetic ancestry, and obesity ORs were estimated in relation to the reference variables indicated. Exposure, health, and symptom ORs were each estimated separately as binary variables. Symptom ORs were estimated as binary variables among symptomatic testers only (Methods). Risk factor adjustments for severity include: sex, age, obesity (Y/N), and underlying health conditions (Y/N if any). Where applicable, individual adjustment variables were omitted to avoid duplicate adjustment (Methods).



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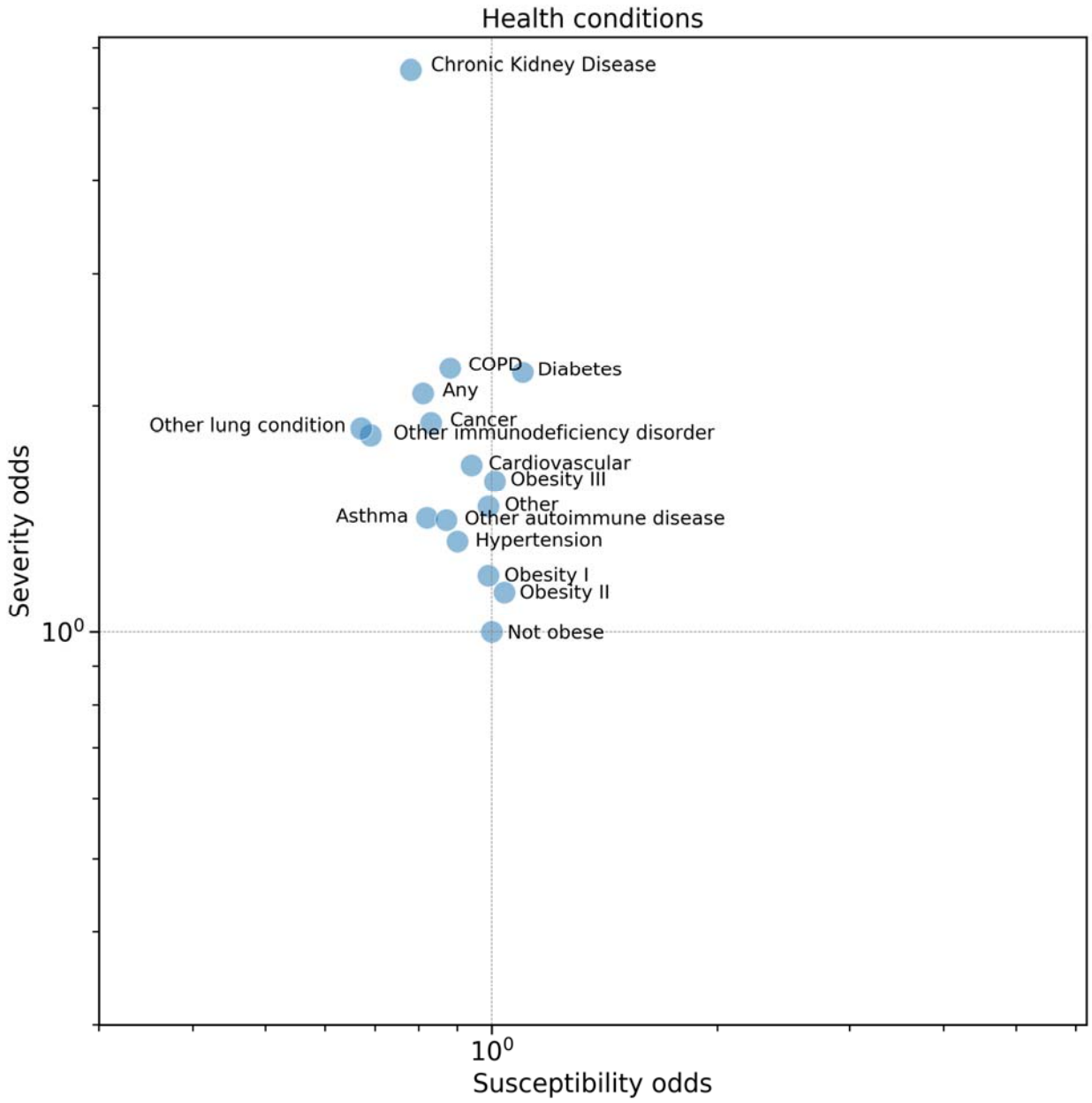

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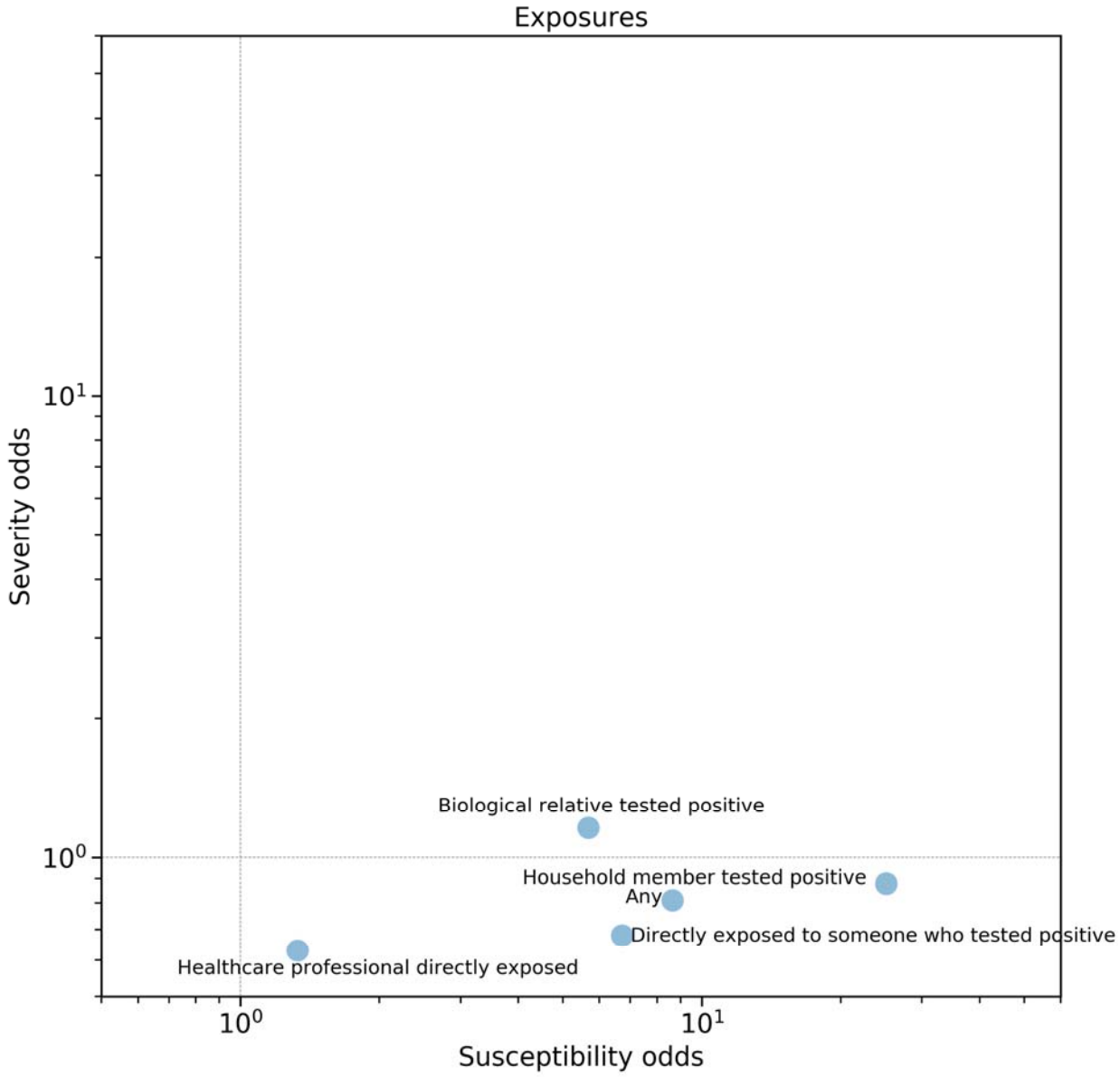

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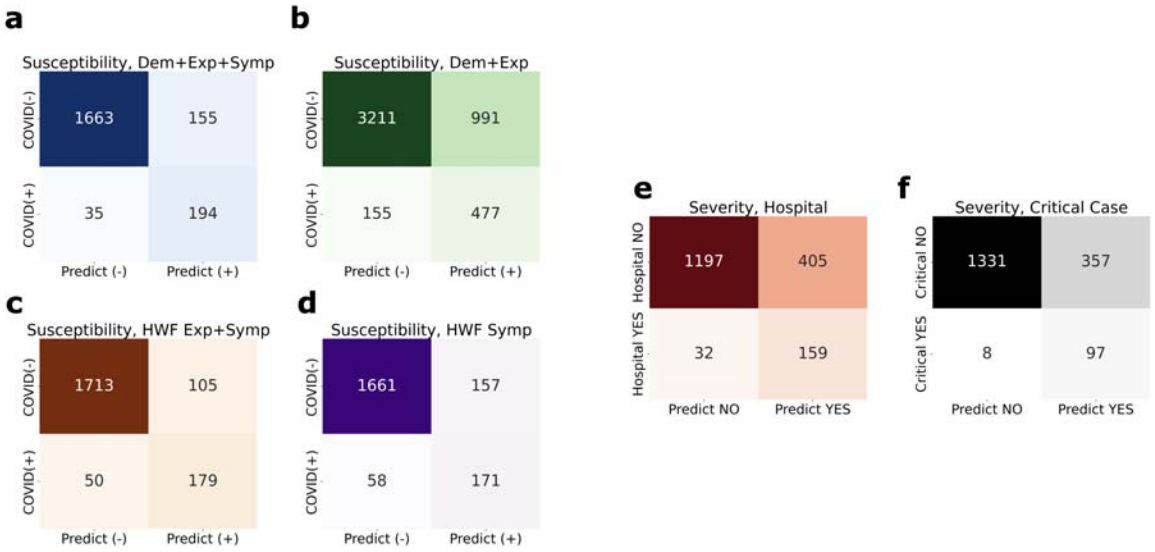
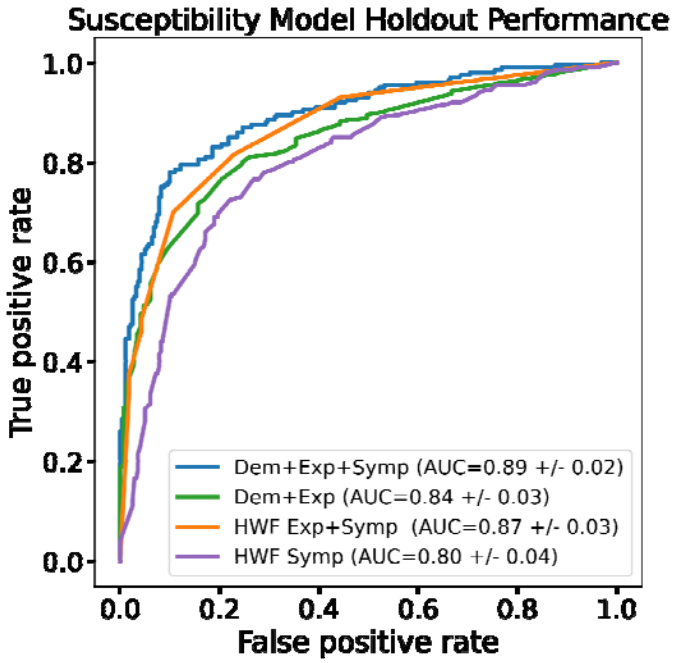
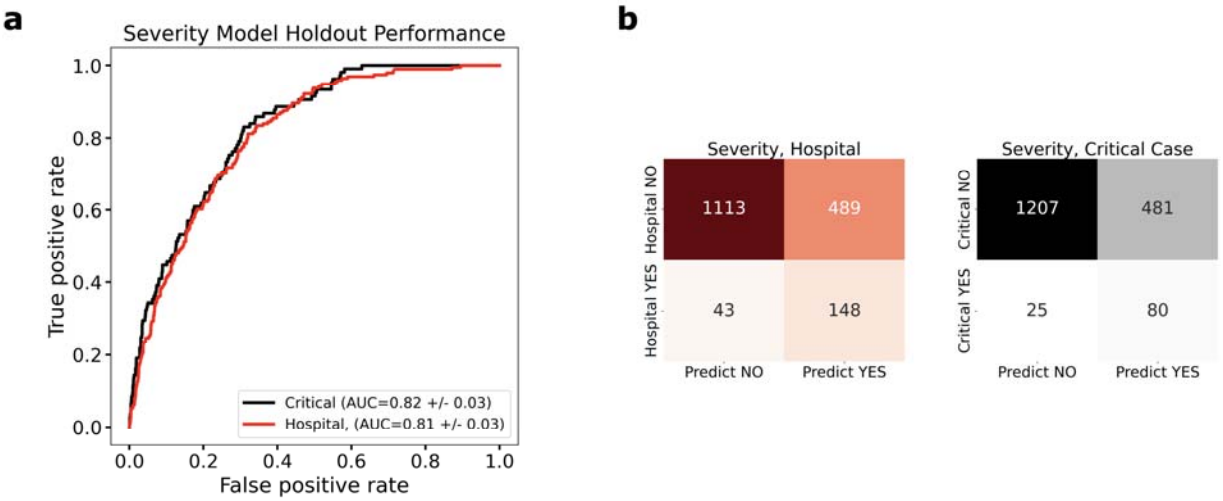
Supplementary Figure 2: Comparison of Susceptibility and Severity adjusted ORs. Comparison of susceptibility ORs (horizontal axis) and severity ORs (vertical axis) from Figures 1 and 2. Severity aORs are for hospitalization. aORs are adjusted as in Figures 1 and 2 (see Fig 3 for adjusted ORs for symptoms). Plotted on a log scale for visibility. (a) **Demographics**, broken down by age, sex, and genetic ancestry. (b) **Health conditions**: Some pre-existing health conditions have increased odds of critical outcomes but susceptibility is not characterized by health conditions. (c) **Exposures** are important for susceptibility but not severity.



854
855 **Supplementary Figure 3: Risk model confusion matrices for independent holdout data.**
856 Numbers represent number of individuals in each category. a) Susceptibility model with
857 demographics, exposures, and symptoms. b) Susceptibility model demographics and exposures
858 (symptoms excluded). c) Literature-based susceptibility model with three risk factors including
859 two exposures and change in taste or smell. d) Literature-based susceptibility model with seven
860 COVID-19 symptoms. e) Hospitalization risk model. f) Critical case risk model. Refer to
861 Methods as well as Supplementary Tables 20-27 for additional model performance data and
862 model risk factor information.



Supplementary Figure 4. Performance of susceptibility models evaluated in a symptomatic cohort of positive and negative testers. Plot depicts receiver operating characteristic (ROC) curves for four susceptibility models (Supplementary Table 20). Here, the modeling cohort has been restricted to positive and negative testers reporting at least one symptom of moderate or greater intensity for model training and evaluation.



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872 **Supplementary Figure 5. Severity Models Excluding Dyspnea (Shortness of Breath).** a)
873 Receiver operating characteristic (ROC) curves for severity models to predict either critical
874 illness progression (black) or hospitalization (red) among COVID-19 positive cases. The models
875 here are built with the same risk factors as in Figure 4 with the exclusion of dyspnea (shortness
876 of breath). b) Classification confusion matrix for severity models. Refer to Methods as well as
877 Supplementary Tables 20 for additional model risk factor information.

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