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Predictors of unrelieved symptoms in *All of Us* Research Program participants with chronic conditions

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Abstract

Context: Over half of American adults are diagnosed with a chronic condition, with an increasing prevalence being diagnosed with multiple chronic conditions. These adults are at higher risk for having unrelieved, co-occurring symptoms, known as symptom clusters.

Objectives: To identify symptom phenotypes of patients diagnosed with four common chronic conditions, specifically, cancer, chronic obstructive pulmonary disease, heart failure, and/or type 2 diabetes mellitus, and to understand factors that predict membership in symptomatic phenotypes.

Methods: We conducted a retrospective, cross-sectional analysis using participant responses (N=14,127) to All of Us Research Program, a National Institutes of Health biomedical database, survey questions. We performed hierarchical clustering to generate symptom phenotypes of fatigue, emotional distress, and pain and used multinomial regression to determine if demographic, healthcare access and utilization, and health-related variables predict symptom phenotype.

Results: Four phenotypes, one asymptomatic or mildly symptomatic and three highly symptomatic (characterized by *severe symptoms*, *severe pain*, and *severe emotional distress*), were identified. The percentage of participants belonging to the *severe symptoms* phenotype increased with the number of chronic conditions. Most notably, foregoing or delaying medical care and rating mental health as *poor* or *fair* increased the odds of belonging to a highly symptomatic phenotype.

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DATA STATEMENT
Data used in this study are from the All of Us Research Hub through the National Institutes of Health. Data was accessed through the Registered Tier and is available to authorized users who have registered with the All of Us Research Program.

DISCLOSURES
The authors declare no conflicts of interest.

Conclusion: We found meaningful relationships between demographic, healthcare access and utilization, and health-related factors and symptom phenotypes. With the increasing trends of American adults with one or more chronic conditions and a demand to individualize care in the precision health era, it is critical to understand the factors that lead to unrelieved symptoms.

Keywords

Signs and symptoms; Cancer; Chronic obstructive pulmonary disease; Heart failure; Type 2 diabetes mellitus; Surveys and questionnaires

INTRODUCTION

In the United States, over half of American adults are diagnosed with a chronic condition, with an increasing prevalence of individuals diagnosed with multiple chronic conditions (1). American adults living with one or more chronic conditions experience a decrease in health-related quality of life and higher overall health-related costs (1,2). Furthermore, these individuals are at higher risk for having unrelieved co-occurring symptoms, known as symptom clusters, related to the chronic condition(s) and/or its treatment that may negatively impact daily life and functional status (3,4). Research suggests that symptom clusters drive both symptom burden and the treatment course across several chronic diseases including breast cancer (5), chronic kidney disease (6), and chronic obstructive pulmonary disease (COPD; 7).

Current trends in disease prevention, management, and treatment take into consideration individual variability in genes, environment, and lifestyle to tailor care to achieve optimal health outcomes; this model of healthcare is defined as precision medicine (8). In line with this model, the goal of symptom science is to identify individuals at risk for symptoms or symptom clusters and develop targeted strategies for preventing symptom occurrence and mitigating symptom severity and burden (4). While the patient symptom experience is highly heterogenous (9–15), prior research specifically aimed a delineating predictors of severe symptom phenotypes is limited, with a small number of studies investigating any particular predictor almost exclusively in cancer populations (16–20). Moreover, research on symptom clusters in individuals diagnosed with multiple chronic conditions, in general, is sparse (17,21,22). It is critical to better understand susceptibilities to symptoms and symptom clusters in individuals diagnosed with one or more chronic conditions.

Large biomedical datasets, like the All of Us Research Program, offer a unique opportunity to study symptom clusters and predictors of symptoms, especially in individuals diagnosed with multiple chronic conditions, at scale (23). The All of Us Research Program includes diverse participants diagnosed with a wide range of conditions allowing for investigation of symptom experiences across various wellness, social, environmental, and economic contexts. We believe that we can leverage All of Us data to generate new knowledge to tailor and improve patient symptom management.

Therefore, the purpose of this study was to identify symptom phenotypes (i.e., characterization of subjective symptom experience) of patients diagnosed with one or more common chronic conditions, specifically cancer, COPD, heart failure, and/or type 2 diabetes mellitus, using All of Us Research Program survey data. Further, we aimed to understand the demographic, healthcare access and utilization, and health-related factors that predict membership to highly symptomatic phenotypes.

METHODS

We conducted a retrospective, cross-sectional analysis using the All of Us Research Program survey data to identify symptom (i.e., fatigue, emotional distress, and pain) phenotypes of patients diagnosed with common chronic conditions (i.e., cancer, COPD, heart failure, and type 2 diabetes) and demographic, healthcare access and utilization, and health-related factors that predict membership to symptomatic phenotypes. This study was exempt from human subjects' approval as only deidentified data were analyzed.

All of Us Research Program

The All of Us Research Program (allofus.nih.gov) is an effort by the National Institutes of Health to gather health data from one million or more diverse individuals living in the United States to accelerate research discoveries that may improve human health. To date, over 315,000 participants have completed the initial steps of the program, which included agreeing to share electronic health records; completing *The Basics*, *Overall Health*, and *Lifestyle* surveys; providing physical measurements; and donating at least one biospecimen. Approved researchers can access the Registered Tier curated dataset of de-identified, individual level electronic health record, survey, physical measurement, and wearable data through the All of Us Research Hub (researchallofus.org).

Cohort Identification

First, we used the Cohort Builder within the All of Us Researcher Workbench to identify all eligible adult (≥18 years of age) participants (n=65,658) diagnosed with cancer (excluding skin and in situ cancer; n=23,983), COPD (including bronchitis and emphysema; n=18,154), heart failure (n=14,449), or type 2 diabetes mellitus (n=35,140) based on condition codes detailed in Appendix A. Then, we limited inclusion to participants who had two or more qualifying codes for a condition and complete responses for the three symptom-related (i.e., fatigue, emotional distress, and pain) items on the *Overall Health* survey on or after the earliest documented condition start date (n=45,907). We further limited inclusion to participants who answered one or more questions on each of *The Basics*, *Overall Health* (beyond the symptom items of interest), and *Health Care Access & Utilization* surveys (N=14,127).

Measures

We used participant responses to survey questions to generate symptom phenotypes and analyze potential predictors of symptomatic phenotypes. Three individual survey questions were used to evaluate participant symptoms of pain, fatigue, and emotional distress, respectively: 1) *In the past 7 days, how would you rate your pain on average?* Response – numeric scale, 0 (no pain) to 10 (worst imaginable pain); 2) *In the past 7 days, how would you rate your fatigue?* Response – 5-point Likert scale (none, mild, moderate, severe, very severe); and 3) *In the past 7 days, how often have you been bothered by emotional problems* *such as feeling anxious, depressed or irritable?* Response – 5-point Likert scale (never, rarely, sometimes, often, always) (24,25). We recoded responses for fatigue and emotional distress to a numeric 0–4 scale, with 4 indicating the worst symptom experience, for analysis purposes. Participants completed symptom questions between June 2016 and July 2020, with all dates systematically shifted backwards by a random number between 1 and 365 by the All of Us Research Program to minimize re-identification risks.

Predictors included demographic, healthcare access and utilization, and health-related variables. For demographics, we included age, gender identity, race/ethnicity, marital status, level of education, insurance status, employment status, and annual household income as potential predictors (26).

Healthcare access and utilization predictors included foregoing and/or delaying medical care, having a usual place for medical care, and time since last seen a health care professional (*About how long has it been since you last saw or talked to a doctor or other health care provider about your own health?*). We defined foregoing and/or delaying medical care as answering “yes” to any of the following three questions: 1) *Have you delayed getting care for any of the following reasons in the past 12 months?*; 2) *During the past 12 months, was there any time when you needed any of the following, but didn’t get it because you couldn’t afford it?*; and 3) *During the past 12 months, were any of the following true for you?* (27–29). We defined not having a usual place for medical care as answering “no” or “don’t know” to the question *Is there a place that you usually go to when you are sick or need advice about your health?* or answering “yes” but indicating going to any location other than a doctor’s office, clinic, or health center most often. Participants who endorsed having “more than one place” were coded as having a usual place for medical care (27–30).

Further, we included three 4-point Likert survey questions that assessed ease of understanding health information (*How often did your doctors or health care providers tell or give you information about your health and health care that was easy to understand?*), being treated with respect by the provider (*How often were you treated with respect by your doctors or health care providers?*), and being asked about opinions or beliefs by the provider (*How often did your doctors or health care providers ask for your opinions or beliefs about your medical care or treatment?*) (27,29). Response options were always, most of the time, some of the time, or none of the time.

Three 5-point Likert scale survey questions were used to evaluate participant general, physical, and mental health, respectively: *In general,* 1) *would you say your health is:*; 2) *how would you rate your physical health?*; and 3) *how would you rate your mental health, including your mood and your ability to think?* (24,25). Response options were excellent, very good, good, fair, or poor.

Data Analysis

All analyses were performed on All of Us data release version 4.0 within the secure Researcher Workbench platform using R (version 4.1.1). First, we generated descriptive statistics and data visualizations to characterize all variables. Because of the substantial number of participants who did not provide responses for the *Health Care Access*

& Utilization survey, we compared demographic and health-related variables between participants with and without these data, using a t-test for age and chi-square tests for all other variables.

Then, we performed hierarchical clustering with Gower's distance (due to ordinality of the symptom survey items) on participant fatigue, emotional distress, and pain scores to create symptom phenotypes. The optimal number of clusters was determined based on the dendrogram. We calculated the percentage of participants that belong to a particular symptom phenotype by chronic condition diagnosis. Finally, we used multinomial regression to determine if demographic, healthcare access and utilization, and health-related variables predict symptom phenotype. Please note that "skipped" is distinct from missing and was included as a response category for many variables. Coefficients were analyzed at a 0.05 significance level.

RESULTS

Participants (*N*=14,127; Figure 1) were approximately 62 years of age and primarily women, White non-Hispanic, married, highly educated, not employed, and insured (Table 1). Compared to participants who completed the *Health Care Access & Utilization* survey, participants who did not complete this survey (*n*=31,780) were younger; were less likely to be White non-Hispanic, married, graduate from college or high school, and employed; have lower household income; and reported poorer health (Table 1). The time between the earliest recorded condition start date for a participant's earliest recorded condition and response to symptom survey items was positively skewed with a mean of 5.41 (*SD*=5.20) years and median of 3.66 (*minimum*=0; *Q1*=1.82, *Q3*=7.48, *maximum*=36.98) years.

Symptom Phenotypes

Four phenotypes, one asymptomatic or mildly symptomatic and three highly symptomatic, were identified (Figure 2). The "mild symptoms" phenotype contains *n*=9,961 participants and is characterized by minimal fatigue, infrequent emotional distress, and mild pain. Within the "mild symptoms" phenotype, approximately 7% (*n*=659) of participants denied all three symptoms. In contrast, the "severe symptoms" phenotype, which contains *n*=618 participants, is characterized by moderate to severe pain, severe fatigue, and frequent emotional distress. The "severe emotional distress" phenotype (*n*=972) is characterized by frequent emotional distress, no to moderate fatigue, and mild pain. The "severe pain" phenotype (*n*=2,576) is characterized by severe pain, mild to moderate fatigue, and infrequent emotional distress. By individual chronic condition (Table 2), a higher percentage of participants diagnosed with cancer (78%) belong to the "mild symptoms" phenotype than the other three conditions (62– 69%). Likewise, a lower percentage of participants diagnosed with cancer belong to the "severe pain" (12%) and "severe symptoms" (3%) phenotypes than the other three conditions (22–25% and 5–6%, respectively). The percentage of participants that belong to the "severe symptoms" phenotype increases with the number of chronic conditions. Approximately 3.96% of participants diagnosed with one condition belong to this phenotype, compared to 5.83% of participants with two conditions, 7.13%

of participants with three conditions, and 8.70% of participants with all four conditions of interest.

Demographic, Healthcare Access and Utilization, and Health-related Factors

Results from the symptom phenotype multinominal regression model are presented in Table 3. Only participants with complete data (n=13,585) were included in the model. In all reported results, the “mild symptoms” phenotype serves as the reference phenotype.

Demographic Factors—In terms of demographic variables, increasing age was associated with lower odds of being in any one of the three highly symptomatic phenotypes (OR=0.97–0.99; all p<0.001). The odds of belonging to the “severe symptoms” or “severe pain” phenotypes were higher for women (OR=1.64, p<0.001; OR=1.47, p<0.001), participants who are not employed (OR=1.52, p=0.002; OR=1.53, p<0.001), and those reporting lower annual household incomes (*see* Table 3). In addition, describing oneself as Black race/non-Hispanic ethnicity (OR=1.42, p<0.001), Hispanic ethnicity (OR=1.39, p=0.001), or other race/ethnicity (OR=1.37, p=0.038) compared to White race/non-Hispanic ethnicity; being divorced (OR=1.17, p=0.039) or cohabitating (OR=1.30, p=0.041) compared to being married; and earning less than a college degree (*see* Table 3) increased the odds of belonging to the “severe pain” phenotype. Marital status (divorced vs. married: OR=1.25, p=0.048; widowed vs. married: OR=1.36, p=0.037) and level of education (1–3 years of college vs. college graduate or greater: OR=0.73, p=0.001) were also associated with membership in the “severe emotional distress” phenotype.

Healthcare Access and Utilization Factors—For healthcare access and utilization variables, the odds of belonging to a highly symptomatic phenotype were greater for participants who had foregone or delayed medical care (OR=1.30–1.68, p<0.001–0.002). The odds of belonging to the “severe pain” (OR=4.33, p=0.023) or “severe symptoms” (OR=21.95, p=0.008) phenotypes were also higher for participants who skipped this question. The odds of belonging to the “severe emotional distress” phenotype were lower for participants who reported that they had not seen a health care professional in over a year compared to the past six months (OR=0.002, p<0.001). Having a usual place for medical care was not associated with symptom phenotype membership; however, the odds of belonging to the “severe symptoms” phenotype were lower for participants who skipped this question compared to participants who positively endorsed having a usual place for medical care (OR=0.01, p<0.001).

Being asked about opinions or beliefs about medical care by the provider *most of the time* (OR=0.78, p<0.001), *some of the time* (OR=0.69, p<0.001), or *none of the time* (OR=0.73, p=0.001) decreased the odds of belonging to the “severe pain” phenotype compared to *always* being asked. Being asked about opinions or beliefs *some of the time* also decreased the odds of belonging to the “severe symptoms” phenotype (OR=0.71, p=0.029). Being treated with respect by the provider *none of the time* increased the odds of belonging to the “severe emotional distress” phenotype (OR=5.82, p=0.042) and decreased the odds of belonging to the “severe symptoms” phenotype (OR=0.04, p<0.001). In addition, being told or given information about health that was easy to understand *some of the time* increased the odds of belonging to the "severe pain" phenotype (*OR*=1.37, *p*=0.011).

Health-related Factors—Notably, the odds of belonging to any of the highly symptomatic phenotypes were higher for participants who rated their mental health as *poor* (*OR*=3.64–39.79, all *p*<0.001) or *fair* (*OR*=1.89–6.44, all *p*<0.001) and lower for participants who rated their mental health as *very good* (*OR*=0.29–0.80, *p*<0.001–0.001) or *excellent* (*OR*=0.10–0.86, *p*<0.001–0.057; please note, rating mental health as *excellent* for the "severe pain" phenotype did not reach statistical significance but trended in the lower odds direction) compared to *good*. Similarly, the odds of belonging to the "severe symptoms" or "severe pain" phenotypes were higher for participants who rated their general or physical health as *poor* (*OR*=1.62–4.18, *p*<0.001–0.001) or *fair* (*OR*=1.16–2.07, *p*<0.001–0.052; please note, rating general health as *fair* for the "severe pain" phenotype did not reach statistical significance but trended in the higher odds direction) compared to *good*. Moreover, *very good* (*OR*=0.30, *p*=0.013) and *excellent* (*OR*=0, *p*<0.001) general health lowered the odds of belonging to the "severe symptoms" phenotype, while *very good* (*OR*=0.65, *p*<0.001) and *excellent* (*OR*=0.52, *p*=0.013) physical health lowered the odds of belonging to the "severe pain" phenotype. The influence of general health and physical health ratings on the "severe emotional distress" phenotype was remarkably different, with *poor* general health (*OR*=0.62, *p*=0.045) decreasing and *very good* (*OR*=1.76, *p*<0.001) and *excellent* (*OR*=2.11, *p*=0.024) physical health increasing the odds of membership.

DISCUSSION

Our analysis illustrates the utility of the All of Us Research Program dataset to advance symptom science research in individuals diagnosed with one or more chronic conditions. Using survey responses for fatigue, emotional distress, and pain, we identified four distinct symptom phenotypes – asymptomatic or mild symptoms, severe emotional distress, severe pain, and severe symptoms – in participants diagnosed with cancer, COPD, heart failure, and/or diabetes. The number of participants that belong to the "severe symptoms" phenotype increases in a direct relationship with the number of chronic conditions. We, further, discovered meaningful relationships between the identified symptom phenotypes and demographic, healthcare access and utilization, and health-related factors.

Most notably, we found that individuals who rated their mental health as *poor* or *fair* had significantly higher odds of belonging to one of the highly symptomatic phenotypes compared to those who rated their mental health as *good*. Likewise, individuals who rated their mental health as *very good* or *excellent* had lower odds of belonging to a highly symptomatic phenotype. While poor mental health may be related to emotional distress, relationships were not limited to the severe emotional distress phenotype. These findings support a growing body of literature which suggests a complex, bidirectional relationship between psychological and physical symptoms in chronic conditions (13,31–33). Given this relationship of mental health with not only the severe emotional distress phenotype but the severe pain and severe symptoms phenotypes as well, mental health interventions such as cognitive behavioral strategies (13,34,35), collaborative care models for mental health and primary care providers (36), and use of telehealth to expand access to mental health services

(37,38) should be explored as methods of symptom management in individuals with chronic conditions.

Consistent with previous research (28), we found that foregoing or delaying medical care was a key factor in unmet health care needs, increasing the likelihood of an individual belonging to one of the phenotypes characterized by severe, unrelieved symptoms. While our analysis did not include information on individuals' reasons for delaying or foregoing medical care, identifying and remedying systemic or interpersonal barriers to receiving care may be a beneficial next step in addressing severe symptom phenotypes. Our analysis also revealed thought-provoking findings related to patient-provider interaction and communication. Specifically, individuals who reported never being treated with respect by a provider had increased odds of belonging to the severe emotional distress phenotype but decreased odds of belonging to the severe symptoms phenotype compared to individuals who reported always being treated with respect. However, caution must be exercised in interpretation of results generated from small numbers of participants. Furthermore, being asked for opinions or beliefs at any frequency other than *always* decreased the odds of belonging to the severe pain phenotype. This may be because participants who feel ignored may be less likely to feel comfortable reporting the true experience of their symptoms.

The observed relationships between healthcare access and utilization and the presence of highly symptomatic phenotypes have the potential to guide intervention. While expansion of health insurance and programs to support cost-saving are important to increasing healthcare utilization, simple interventions aimed at clinicians could support decreased symptom burden. Existing literature suggests that breakdowns in patient-provider communication, including feeling dismissed or the lack of an open relationship, can negatively impact the management of chronic conditions (39,40). How these aspects of patient-provider interaction and communication impact symptom management and subsequent outcomes requires further investigation.

Characterization of the relationship between symptom phenotypes and the patient-provider relationship may be a critical step in addressing racial disparities in symptom burden. In line with prior literature (41), we found that those who report their race/ethnicity as Black/non-Hispanic, Hispanic/any race, or other have a higher risk of experiencing more severe symptom phenotypes compared to individuals who report their race/ethnicity as White/non-Hispanic. Given our results relating foregoing or delaying medical care and patient-provider interaction and communication to symptomatic phenotypes, lack of care and/or suboptimal patient-provider interaction and communication may be contributing to disparities in symptom outcomes. Some research shows that racial concordance between the patient and physician can impact communication (42). Additionally, evidence suggests that failure to attend to culturally specific and informational needs in patients who belong to historically marginalized groups can lead to lower trust and harm the patient-provider relationship (43). While research in this area is sparse, it has the potential to move symptom science from the characterization of disparities to potential interventions targeting patient-provider interaction and communication. This line of investigation would complement research on the reduction of systemic inequities to address racism in healthcare at both a systemic and interpersonal level. Interpretation of these results in a way that identifies actionable targets is supported by Critical Race Theory, which emphasizes a movement from characterization of disparities to identifying potential mechanisms of eliminating them (44). Incorporation of additional surveys within the All of Us Research Program capturing more encompassing social determinants of health may allow for future analysis addressing these issues more thoroughly.

There are several limitations to our analysis using the All of Us Research Program data. First, we focused on four common chronic conditions. Generalizability of our findings to other chronic conditions is unknown. Second, because the *Health Care Access & Utilization* survey is not required for enrollment, there may be differences in participants who completed the survey and those who did not, again, potentially impacting the generalizability of results. In addition, geographical factors (i.e., urban versus rural, proximity to academic medical center) were not available for participants. Third, the analysis focused on the three symptoms evaluated with All of Us surveys. Given that these three symptoms are often clustered with other symptoms, such as sleep disturbance, nausea, anxiety, and depression in chronic conditions (11,45,46), identified symptom phenotypes may be characterized by additional symptoms. Likewise, evaluated predictors may be associated with additional symptoms.

Building on these limitations for future research, we encourage the addition of more symptom information to the All of Us Research Program dataset and other large biomedical databases. Incoming genomic information will allow for the exploration of an additional dimension of symptom science precision medicine, the biological underpinnings of symptoms and symptom clusters with shared etiology (47). The results of this study, as well as future analyses of symptom clusters using All of Us data, may identify targets for symptom management interventions at the biological, interpersonal, and systemic levels.

Conclusion

The objective of this study was to understand the factors that contribute to unrelieved symptoms in All of Us participants diagnosed with one or more common chronic conditions. We report relationships between demographic, healthcare access and utilization, and health-related factors and four symptom phenotypes. All of Us Research Program data offers a unique opportunity to study symptoms in individuals diagnosed with one or more chronic conditions and inform targeted interventions to mitigate symptom burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY MESSAGE

This article describes demographic, healthcare access and utilization, and health-related factors that predict symptom phenotypes in the All of Us Research Program, a National Institutes of Health biomedical database, dataset. Our results indicate distinct symptom phenotypes that can be leveraged for future intervention.

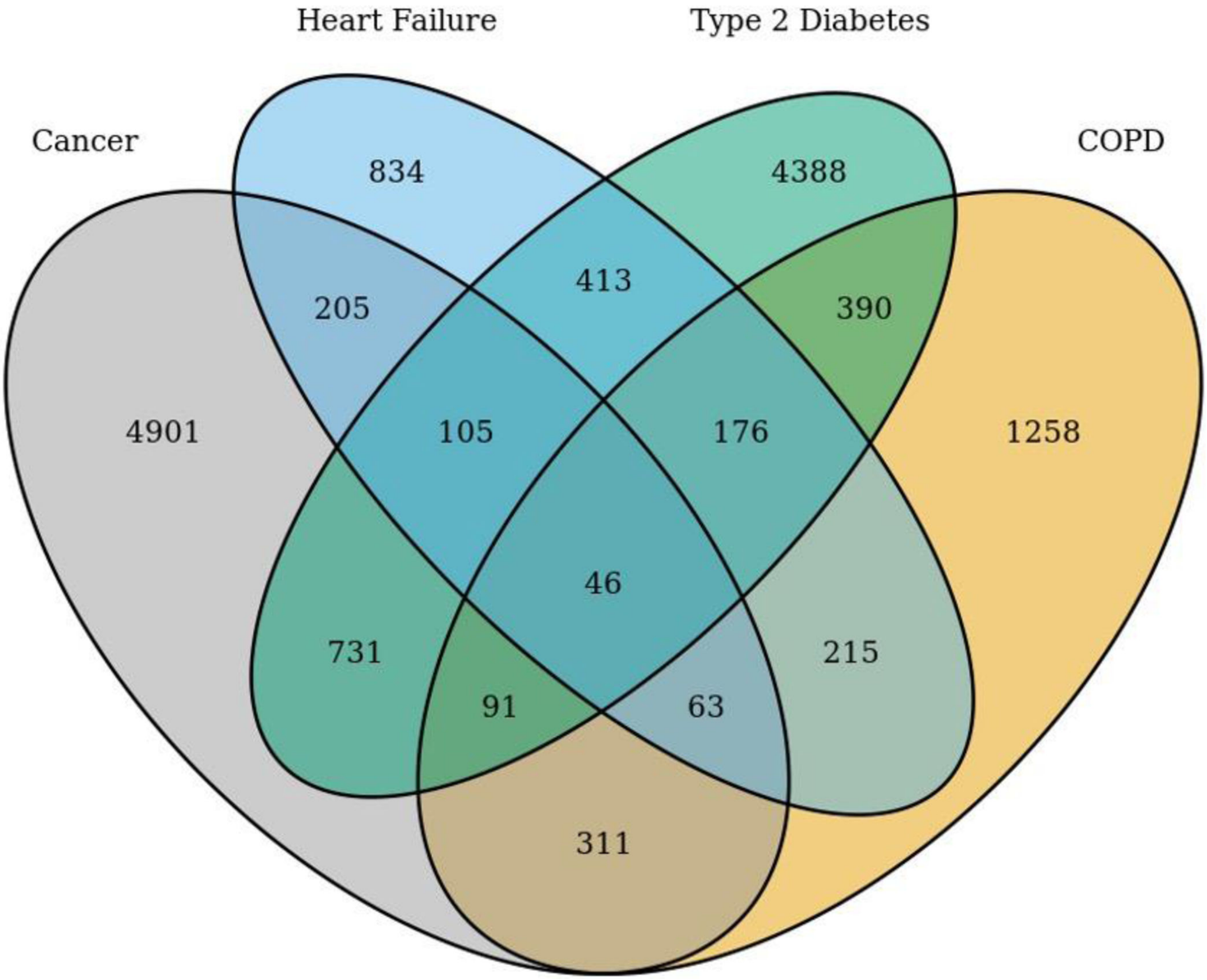

Figure 1.

Chronic condition diagnoses in study participant cohort (*N*=14,127).

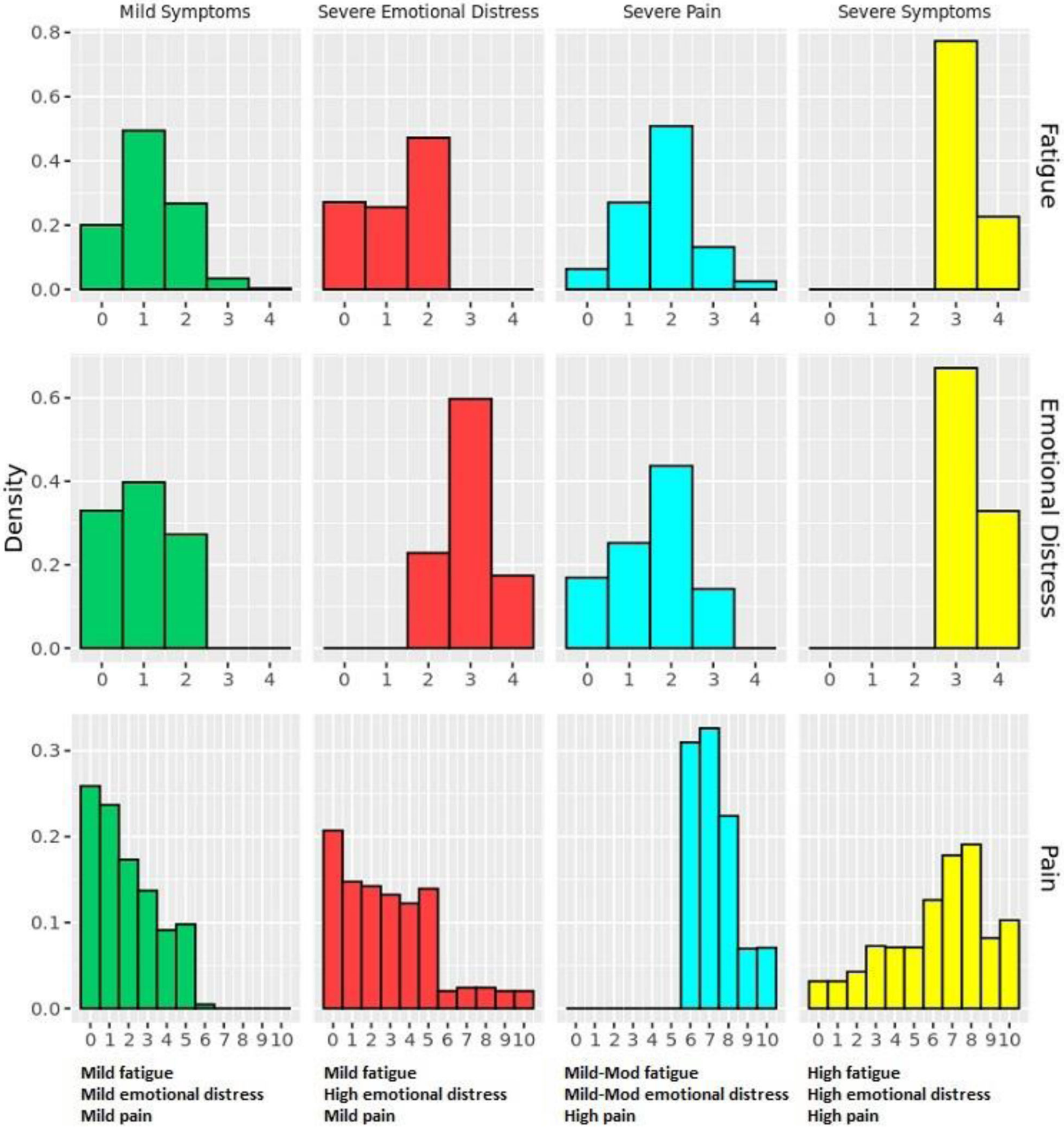

Figure 2.

Chronic condition symptom phenotypes. *The x-axis represents the survey response scale for each symptom. The higher the value, the more severe the symptom. Mod=moderate.*

Table 1.

Comparison of demographic- and health-related variables between participants with and without Health Care Access & Utilization survey information

	With information (*N*=14,127)	**Without information (*N*=31,780)**
	Mean (SD) or n (%)	**Mean (SD) or n (%)**
Age (years)	62.32 (12.22)	60.24 (13.01)
Gender identity		
Woman	8,280 (58.61)	17,877 (56.25)
Man	5,692 (40.29)	13,301 (41.85)
Other/skipped	155 (1.10)	602 (1.89)
Race/ethnicity		
Asian/non-Hispanic	238 (1.71)	588 (1.88)
Black/non-Hispanic	1,588 (11.39)	8,535 (27.29)
White/non-Hispanic	10,586 (75.92)	14,289 (45.69)
Hispanic/any race	956 (6.86)	6,262 (20.02)
Other	352 (2.52)	925 (2.96)
Skipped	223 (1.60)	675 (2.16)
Marital status		
Married	7,813 (55.31)	12,039 (37.88)
Divorced	2,254 (15.96)	6,436 (20.25)
Cohabiting	524 (3.84)	1,248 (3.93)
Never married	1,957 (13.85)	6,413 (20.18)
Separated	297 (2.10)	1,549 (4.87)
Widowed	1,125 (7.96)	3,206 (10.09)
Skipped	139 (0.98)	889 (2.80)
Education level		
College graduate or >	7,708 (54.56)	8,712 (27.41)
1–3 years of college	3,950 (27.96)	9,053 (28.49)
High school or GED	1,770 (12.53)	8,162 (25.68)
< High school degree	589 (4.17)	5,001 (15.74)
Skipped	110 (0.78)	852 (2.68)
Insurance		
Yes	13,685 (97.78)	28,575 (95.83)
No	311 (2.22)	1,244 (4.17)
Employment status		
Employed	4,966 (35.52)	7,301 (24.62)
Not employed	9,016 (64.48)	22,357 (75.38)
Annual household income		
< $10,000	975 (6.90)	5,877 (18.49)
$10,000 - $25,000	1,717 (12.15)	5,691 (17.91)

	With information **(*N*=14,127)**	**Without information** **(*N*=31,780)**
	Mean (SD) or n (%)	**Mean (SD) or n (%)**
$25,000 - $35,000	1,045 (7.40)	2,381 (7.49)
$35,000 - $50,000	1,291 (9.14)	2,218 (6.98)
$50,000 - $75,000	1,968 (13.93)	2,548 (8.02)
$75,000 - $100,000	1,576 (11.16)	1,584 (4.98)
$100,000 - $150,000	1,933 (13.68)	1,700 (5.35)
$150,000 - $200,000	857 (6.07)	616 (1.94)
> $200,000	1,213 (8.59)	848 (2.67)
Skipped	1,552 (10.99)	8,317 (26.17)
General health		
Poor	790 (5.59)	3,892 (12.25)
Fair	3,365 (23.82)	10,671 (33.58)
Good	5,217 (36.93)	10,765 (33.87)
Very good	3,885 (27.50)	4,964 (15.62)
Excellent	798 (5.65)	1,179 (3.71)
Skipped	72 (0.51)	309 (0.97)
Physical health		
Poor	909 (6.43)	3,737 (11.76)
Fair	3,563 (25.22)	10,855 (34.16)
Good	5,241 (37.10)	10,913 (34.34)
Very good	3,603 (25.50)	4,580 (14.41)
Excellent	716 (5.07)	1,121 (3.53)
Skipped	95 (0.67)	574 (1.81)
Mental health		
Poor	286 (2.02)	1,301 (4.09)
Fair	1,584 (11.21)	5,668 (17.84)
Good	3,586 (25.38)	10,094 (31.76)
Very good	5,049 (35.74)	8,367 (26.33)
Excellent	3,540 (25.06)	5,951 (18.73)
Skipped	82 (0.58)	399 (1.26)
Cancer		
Yes	6,453 (45.68)	9,606 (30.23)
No	7,674 (54.32)	22,174 (69.77)
COPD		
Yes	2,550 (18.05)	7,943 (24.99)
No	11,577 (81.95)	23,837 (75.01)
Heart Failure		
Yes	2,057 (14.56)	6,813 (21.44)
No	12,070 (85.44)	24,967 (78.56)
Type 2 Diabetes Mellitus		

	With information (*N*=14,127)	Without information (*N*=31,780)
	Mean (SD) or n (%)	**Mean (SD) or n (%)**
Yes	6,340 (44.88)	18.040 (56.77)
No	7,787 (55.12)	13,740 (43.23)
Number of conditions		
1	11,381 (80.56)	23,276 (73.24)
2	2,265 (16.03)	6,606 (20.79)
3	435 (3.08)	1,678 (5.28)
4	46 (0.33)	220 (0.69)

Note. All p-values <0.001. COPD=chronic obstructive pulmonary disease.

Table 2.

Percentage of participants belonging to a symptom phenotype by chronic condition diagnosis

	Symptom Phenotype			
%	**Mild symptoms**	**Severe emotional distress**	**Severe pain**	**Severe symptoms**
Cancer	78.0	6.7	12.4	2.9
COPD	61.9	6.7	25.2	6.2
Heart failure	68.6	4.7	21.8	4.9
Type 2 diabetes mellitus	64.0	7.1	22.8	6.0

Note. Percentages add to 100% row-wise across the chronic conditions. Participants can be diagnosed with multiple chronic conditions. COPD=chronic obstructive pulmonary disease.

Table 3

Odds Ratios for Demographic, Healthcare Access and Utilization, and Health-related Factors From the Symptom Phenotype Multinomial Regression Model.

			Phenotype[a]			
	Severe Emotional Distress		**Severe Pain**		**Severe Symptoms**	
	OR (95 CI)	***P*-value**	**OR (95 CI)**	***P*-value**	**OR (95 CI)**	**p-value**
Demographic factors						
Age (yrs)	0.98 (0.97–0.98)	<0.001[b]	0.99 (0.99–0.995)	<0.001[b]	0.97 (0.96 – 0.98)	<0.001[b]
Gender identity						
Woman	1.08 (0.92–1.27)	0.325	1.47 (1.32–1.64)	<0.001[b]	1.64 (1.30 – 2.07)	<0.001[b]
Other/skipped	1.51 (0.81–2.81)	0.196	1.51 (0.94–2.43)	0.091	0.72 (0.27 – 1.94)	0.514
Man (reference)						
Race/ethnicity						
Asian/non-Hispanic	0.55 (0.29–1.06)	0.074	1.23 (0.83–1.81)	0.298	0.64 (0.25 – 1.63)	0.351
Black/non-Hispanic	0.83 (0.64–1.07)	0.152	1.42 (1.22–1.65)	<0.001[b]	1.16 (0.87 – 1.56)	0.305
Hispanic/any race	0.98 (0.73–1.32)	0.905	1.39 (1.15–1.68)	0.001[b]	1.32 (0.95 – 1.85)	0.103
Other	0.92 (0.57–1.49)	0.747	1.37 (1.02–1.85)	0.038[b]	1.22 (0.67 – 2.22)	0.517
Skipped	1.17 (0.65–2.14)	0.599	1.05 (0.69–1.61)	0.829	0.70 (0.23 – 2.10)	0.519
White/non-Hispanic (reference)						
Marital status						
Divorced	1.25 (1.00–1.56)	0.048[b]	1.17 (1.01–1.35)	0.039[b]	1.15 (0.86 – 1.53)	0.338
Cohabiting	0.99 (0.67–1.46)	0.938	1.30 (1.01–1.66)	0.041[b]	0.73 (0.42 – 1.26)	0.256
Never married	1.18 (0.94–1.47)	0.156	1.07 (0.91–1.25)	0.404	0.78 (0.58 – 1.06)	0.118
Separated	0.88 (0.52–1.50)	0.640	1.29 (0.94–1.77)	0.113	1.11 (0.66 – 1.87)	0.698
Widowed	1.36 (1.02–1.82)	0.037[b]	0.97 (0.80–1.18)	0.788	1.06 (0.70 – 1.60)	0.793
Skipped	1.08 (0.48–2.43)	0.851	1.55 (0.95–2.51)	0.077	1.49 (0.63 – 3.52)	0.360
Married (reference)						
Education level						
1–3 years of college	0.73 (0.60–0.88)	0.001[b]	1.36 (1.20–1.53)	<0.001[b]	1.21 (0.94 – 1.55)	0.146
High school or GED	0.94 (0.74–1.20)	0.605	1.58 (1.36–1.85)	<0.001[b]	1.09 (0.80 – 1.50)	0.574
< High school degree	0.90 (0.62–1.32)	0.600	1.37 (1.07–1.76)	0.013[b]	0.82 (0.52 – 1.28)	0.378
Skipped	1.05 (0.45–2.47)	0.915	1.17 (0.66–2.09)	0.586	2.13 (0.85 – 5.35)	0.107
College graduate or > (reference)						
Insurance						
No	1.45 (0.94–2.24)	0.091	0.94 (0.69–1.29)	0.712	1.43 (0.88 – 2.32)	0.151
Yes (reference)						
Employment status						
Not employed	0.96 (0.80–1.14)	0.619	1.53 (1.35–1.73)	<0.001[b]	1.52 (1.17 – 1.97)	0.002[b]
Employed (reference)						

			Phenotype[a]			
	Severe Emotional Distress		**Severe Pain**		**Severe Symptoms**	
	OR (95 CI)	***P*-value**	**OR (95 CI)**	***P*-value**	**OR (95 CI)**	**p-value**
Annual household income						
< $10,000	1.40 (0.98–2.02)	0.067	2.19 (1.72–2.78)	<0.001[b]	2.09 (1.32 – 3.32)	0.002[b]
$10,000–$25,000	1.18 (0.88–1.59)	0.276	1.59 (1.31–1.94)	<0.001[b]	1.61 (1.07 – 2.44)	0.024[b]
$25,000–$35,000	1.05 (0.76–1.47)	0.759	1.32 (1.06–1.64)	0.013[b]	1.68 (1.07 – 2.63)	0.025[b]
$35,000–$50,000	1.16 (0.85–1.59)	0.339	1.18 (0.95–1.45)	0.135	1.61 (1.01 – 2.56)	0.045[b]
$75,000–$100,000	0.95 (0.69–1.31)	0.758	1.23 (0.99–1.51)	0.057	1.12 (0.66 – 1.90)	0.680
$100,000–$150,000	0.92 (0.69–1.25)	0.600	0.93 (0.75–1.15)	0.484	1.02 (0.61 – 1.71)	0.941
$150,000–$200,000	1.00 (0.69–1.46)	0.998	0.87 (0.64–1.18)	0.367	1.22 (0.59 – 2.54)	0.595
> $200,000	1.19 (0.85–1.68)	0.318	0.88 (0.67–1.17)	0.372	0.57 (0.22 – 1.45)	0.235
Skipped	1.29 (0.95–1.77)	0.103	1.54 (1.26–1.88)	<0.001[b]	1.85 (1.17 – 2.92)	0.008[b]
$50,000–$75,000 (reference)						
Healthcare access and utilization factors						
Foregoing or delaying medical care						
Yes	1.30 (1.10–1.53)	0.002[b]	1.32 (1.18–1.46)	<0.001[b]	1.68 (1.31 – 2.16)	<0.001[b]
Skipped	2.04 (0.24–17.12)	0.512	4.33 (1.22–15.30)	0.023[b]	21.95 (2.24 – 215.30)	0.008[b]
No (reference)						
Usual place for medical care						
No	1.08 (0.86–1.37)	0.502	1.15 (0.98–1.34)	0.082	1.29 (0.97 – 1.72)	0.080
Skipped	2.30 (0.41–12.97)	0.344	1.63 (0.49–5.44)	0.427	0.01 (0.01 – 0.01)	<0.001[b]
Yes (reference)						
Last seen by health care professional						
6 months–1 year	0.88 (0.63–1.24)	0.474	0.83 (0.64–1.08)	0.161	0.81 (0.46 – 1.44)	0.473
> 1 year	0.002 (0.002–0.002)	<0.001[b]	1.02 (0.36–2.90)	0.975	3.24 (0.72 – 14.57)	0.125
Skipped/Don’t know	0.66 (0.28–1.52)	0.325	1.21 (0.75–1.93)	0.435	1.45 (0.62 – 3.43)	0.393
≤6 months (reference)						
Ease of understanding health information						
Most of the time	0.86 (0.72–1.03)	0.099	1.03 (0.91–1.17)	0.612	0.97 (0.76 – 1.24)	0.808
Some of the time	0.99 (0.69–1.40)	0.937	1.37 (1.08–1.74)	0.011[b]	1.23 (0.81 – 1.87)	0.333
None of time	0.80 (0.30–2.15)	0.664	1.02 (0.52–1.98)	0.964	1.11 (0.36 – 3.39)	0.860
Skipped/Don’t know	0.94 (0.50–1.78)	0.852	0.84 (0.54–1.31)	0.445	0.70 (0.27 – 1.82)	0.469
Always (reference)						
Treated with respect by the provider						
Most of the time	1.06 (0.87–1.30)	0.572	1.13 (0.99–1.30)	0.082	1.18 (0.91 – 1.53)	0.210
Some of the time	1.01 (0.63–1.61)	0.974	1.27 (0.92–1.75)	0.150	1.17 (0.70 – 1.95)	0.542
None of time	5.82 (1.06–31.90)	0.042[b]	1.56 (0.37–6.63)	0.547	0.04 (0.04 – 0.04)	<0.001[b]
Skipped/Don’t know	0.89 (0.43–1.84)	0.745	1.16 (0.75–1.79)	0.494	0.63 (0.24 – 1.62)	0.336
Always (reference)						

			Phenotype[a]			
	Severe Emotional Distress		**Severe Pain**		**Severe Symptoms**	
	OR (95 CI)	***P*-value**	**OR (95 CI)**	***P*-value**	**OR (95 CI)**	**p-value**
Asked opinion/beliefs by provider						
Most of the time	0.86 (0.70–1.06)	0.161	0.78 (0.68–0.89)	<0.001[b]	0.90 (0.68 – 1.19)	0.453
Some of the time	0.88 (0.70–1.09)	0.242	0.69 (0.59–0.80)	<0.001[b]	0.71 (0.52 – 0.97)	0.029[b]
None of time	1.19 (0.92–1.54)	0.191	0.73 (0.60–0.87)	0.001[b]	0.87 (0.60 – 1.27)	0.476
Skipped/Don’t know	1.56 (1.00–2.45)	0.0497[b]	0.99 (0.72–1.35)	0.939	0.85 (0.43 – 1.68)	0.644
Always (reference)						
Health-related factors						
General health						
Poor	0.62 (0.39–0.99)	0.045[b]	1.62 (1.22–2.16)	0.001[b]	2.96 (1.90 – 4.62)	<0.001[b]
Fair	0.98 (0.76–1.24)	0.837	1.16 (1.00–1.36)	0.052	1.51 (1.10 – 2.08)	0.012[b]
Very good	1.13 (0.84–1.52)	0.414	0.88 (0.72–1.08)	0.232	0.30 (0.12 – 0.78)	0.013[b]
Excellent	1.03 (0.56–1.91)	0.924	0.64 (0.39–1.03)	0.065	0 (0 – 0)	<0.001[b]
Skipped	1.07 (0.38–3.00)	0.893	0.94 (0.44–1.98)	0.862	1.17 (0.24 – 5.73)	0.850
Good (reference)						
Physical health						
Poor	1.92 (1.27–2.90)	0.002[b]	2.53 (1.92–3.33)	<0.001[b]	4.18 (2.67 – 6.56)	<0.001[b]
Fair	1.12 (0.88–1.42)	0.374	1.68 (1.44–1.95)	<0.001[b]	2.07 (1.48 – 2.91)	<0.001[b]
Very good	1.76 (1.30–2.38)	<0.001[b]	0.65 (0.52–0.80)	<0.001[b]	0.83 (0.32 – 2.15)	0.704
Excellent	2.11 (1.10–4.02)	0.024[b]	0.52 (0.32–0.87)	0.013[b]	1.74 (0.22 – 13.85)	0.601
Skipped	0.82 (0.27–2.45)	0.718	1.42 (0.82–2.45)	0.214	1.43 (0.43 – 4.75)	0.558
Good (reference)						
Mental health						
Poor	24.10 (14.05–41.34)	<0.001[b]	3.64 (2.10–6.31)	<0.001[b]	39.79 (22.86 – 69.24)	<0.001[b]
Fair	4.73 (3.88–5.78)	<0.001[b]	1.89 (1.60–2.23)	<0.001[b]	6.44 (4.99 – 8.33)	<0.001[b]
Very good	0.29 (0.24–0.36)	<0.001[b]	0.80 (0.70–0.91)	0.001[b]	0.35 (0.24 – 0.52)	<0.001[b]
Excellent	0.10 (0.07–0.13)	<0.001[b]	0.86 (0.74–1.00)	0.057	0.16 (0.08 – 0.33)	<0.001[b]
Skipped	0.73 (0.28–1.87)	0.505	1.27 (0.68–2.37)	0.456	5.63 (2.35 – 13.53)	<0.001[b]
Good (reference)						

Note. OR=odds ratio; 95CI=95% confidence interval.

[a] The “mild symptoms” phenotype is the reference phenotype.

[b] $P<0.05$