

## Original article

# Anxiety, depression and quality of life in relation to SARS-CoV-2 antibodies in individuals living with diabetes during the second wave of COVID-19



Lind Alexander<sup>a,\*</sup>, Cao Yang<sup>b,c</sup>, Hesser Hugo<sup>d,e</sup>, Hårdstedt Maria<sup>f,g,h</sup>, Jansson Stefan<sup>i,j</sup>, Lernmark Åke<sup>a</sup>, Sundqvist Martin<sup>f</sup>, Tevell Staffan<sup>f,k</sup>, Tsai Cheng-ting<sup>l</sup>, Wahlberg Jeanette<sup>f</sup>, Jendle Johan<sup>f</sup>

<sup>a</sup> Department of Clinical Sciences Malmö, Lund University, Sweden

<sup>b</sup> Clinical Epidemiology and Biostatistics, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

<sup>c</sup> Unit of Integrative Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

<sup>d</sup> School of Behavioural, Social and Legal Sciences, Center for Health and Medical Psychology, Örebro University, Sweden

<sup>e</sup> Department of Behavioural Sciences and Learning, Linköping University, Linköping, Sweden

<sup>f</sup> School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Sweden

<sup>g</sup> Center for Clinical Research Dalarna, Uppsala University, Falun, Sweden

<sup>h</sup> Vansbro Primary Health Care Center, Vansbro, Sweden

<sup>i</sup> School of Medical Sciences, University Health Care Research Centre, Örebro University, Örebro, Sweden

<sup>j</sup> Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

<sup>k</sup> Department of Infectious Diseases, Karlstad Hospital and Centre for Clinical Research and Education, Region Värmland, Karlstad, Sweden

<sup>l</sup> Enable Biosciences Inc., South San Francisco, CA, United States of America

## ARTICLE INFO

## Article History:

Received 27 October 2023

Revised 12 December 2023

Accepted 13 December 2023

Available online 15 December 2023

## Keywords:

Diabetes  
SARS-CoV-2  
COVID-19  
Anxiety  
Depression  
Quality of life  
Virus antibodies

## ABSTRACT

**Aims:** The objective was to compare anxiety, depression, and quality of life (QoL) in individuals living with type 1 (T1D) and type 2 (T2D) diabetes with matched controls during the second wave of the COVID-19 pandemic.

**Methods:** Via randomization, individuals living with diabetes T1D ( $n = 203$ ) and T2D ( $n = 413$ ), were identified during February–July 2021 through health-care registers. Population controls ( $n = 282$ ) were matched for age, gender, and residential area. Questionnaires included self-assessment of anxiety, depression, QoL, and demographics in relation to SARS-CoV-2 exposure. Blood was collected through home-capillary sampling, and SARS-CoV-2 Nucleocapsid (NCP) and Spike antibodies (SC2\_S1) were determined by multiplex Antibody Detection by Agglutination-PCR (ADAP) assays.

**Results:** Younger age and health issues were related to anxiety, depression, and QoL, with no differences between the study groups. Female gender was associated with anxiety, while obesity was associated with lower QoL. The SARS-CoV-2 NCP seroprevalence was higher in T1D (8.9 %) compared to T2D (3.9 %) and controls (4.0 %), while the SARS-CoV-2 SC2\_S1 seroprevalence was higher for controls (25.5 %) compared to T1D (16.8 %) and T2D (14.0 %).

**Conclusions:** A higher SARS-CoV-2 infection rate in T1D may be explained by younger age and higher employment rate, and the associated increased risk for viral exposure.

© 2023 The Author(s). Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared by the World Health Organization (WHO) in March

2020 [1]. As of January 2023, there are over 663 million confirmed cases of COVID-19 and over 6.7 million deaths globally reported to the WHO [1].

Outbreaks of infections have historically been associated with a range of psychosocial impacts on individual as well as on community levels, recent examples include the epidemics of SARS-CoV [2] and Ebola [3] as well as the H1N1/A influenza pandemic [4]. It is well established that the emergence of the COVID-19 pandemic and its subsequent consequences including high mortality rates and

\* Corresponding author at: Department of Clinical Sciences Malmö, Lund University CRC, Jan Waldenströmsgata 35, Skåne University Hospital, SE-21428 Malmö, Sweden.  
E-mail address: [Alexander.lind@med.lu.se](mailto:Alexander.lind@med.lu.se) (L. Alexander).

lockdowns, caused increased psychosocial worries in the society [5–9]. In Germany, a large cohort study found increased stress in all age-groups, with depression and anxiety predominantly in younger age-groups during the initial phase of the pandemic as compared to baseline examination 1–5 years earlier [10]. An association between distress and younger age was reported from both the UK and US [6,7]. A survey in China, the origin country of the COVID-19 pandemic [11], found that individuals with chronic illness compared to the general population reported increased stress, anxiety and depression during the early outbreaks of the pandemic [12]. In Sweden, diabetes was early characterized as an additional risk factor after COVID-19 infection but without distinction between type 1 (T1D) or type 2 (T2D) diabetes. A meta-analysis reported diabetes to be associated with increased mortality (1.9 times) and severe illness (2.75 times) in association with COVID-19 infection [13].

In this study, we aimed to determine the psychosocial impact (i.e., anxiety, depression and quality of life (QoL)) in individuals living with T1D and T2D compared to the general population also in association with seroprevalence of SARS-CoV-2 antibodies. The psychosocial impact of the COVID-19 pandemic on individuals living outside major metropolitan areas in Sweden has to our knowledge not been reported previously. We speculate that restrictions might have reduced the QoL in the population in general during the pandemic, and in subgroups of individuals according to sociodemographic variables rather than in individuals living with diabetes. A hypothesis is therefore that the pandemic did not result in reduced QoL in individuals living with diabetes, despite the communication of increased risk of disease-related complications in this group.

Specifically, the aims were to determine:

- 1) The psychosocial well-being during the COVID-19 pandemic in early 2021 in individuals living with T1D, T2D, and matched population controls;
- 2) SARS-CoV-2 antibodies as a measure of the cumulative incidence of COVID-19 infection in both urban and rural areas of Sweden.

## Methods

### Study-population

The study included participants from the regions of Dalarna, Värmland, and Örebro in Sweden, which in 2020, had an estimated total population of 877,000 residents living in this region. Sample collection was performed from February to July 2021. The study protocol included a two-step process for participation. First, letters including informed consents were mailed out to all prospective participants. Second, when correctly signed informed consents were received, questionnaires and kits for home-capillary blood sampling were mailed.

### Questionnaires

All study participants were asked to answer four questionnaires. These questionnaires were either mailed and answered on paper or answered through e-mail from the RedCap database. Questionnaires included standardized measures for:

- 1) Anxiety (Generalized Anxiety Disorder Assessment (GAD-7)) [14–16],

The self-reported survey assesses symptoms of anxiety during the two past weeks, it includes 7 items on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day). The items are summed to a total score in the survey in the range from 0 to 21, with scores of 5, 10 and 15 representing mild, moderate, and severe anxiety symptoms respectively.

- 2) Depression (Montgomery Åsberg Depression Rating Scale (MADRS-S)) [17–19],

The self-reported survey includes 9 items, each scored from 0 to 6, and with a total sum of 0–54. Cut-off scores 0–12, 13–19, 20–34 and  $\geq 34$  define levels of depression to minimal, mild, moderate, and severe, respectively. The items included are related to sadness, sleep, appetite, concentration, pessimism, suicidal thoughts, inner tension, lassitude, and inability to feel.

- 3) Quality of life (Brunnsviken-Brief Quality of life scale (BBQ)) [20],

The survey is a brief assessment of QoL including 12 items in 6 different areas: creativity, friends and friendship, learning, philosophy of life, recreation, and view on self. Two items cover each area with one assessing satisfaction and the other assessing importance. Each item in the survey is assessed on a 5-point Likert scale with a scoring range from 0 (strongly disagree) to 4 (strongly agree). The total score is obtained by multiplying the satisfaction (item 1,3,5,7,9,11) with the importance (item 2,4,6,8,10,12) within each area and then adding these 6 values together. The range of the total score is from 0 to 96 with a higher score representing an assessment of higher QoL. A previous mean score in the Swedish general population was reported to 60.1 [20].

- 1) A fourth questionnaire was used to obtain general information as well as to include reflection on the ongoing SARS-CoV-2 pandemic. Questions included:

- Demographic variables in age, gender, marital status, education level and employment status
- Health
- Social variables in smoking and alcohol use
- Clinical variables in perceived health and body mass index (BMI)
- Pandemic-related variables on vaccine status, adherence to guidelines and history of previous infection

### SARS-CoV-2 antibodies

Plasma samples were analyzed using a custom modified Hamilton Microlab ADAP STAR hands-free automated liquid-handling platform (Hamilton, Bonaduz, Switzerland) [21–25]. SARS-CoV-2 NCP and SC2\_S1 antibodies were determined in a multiplex assay. Synthesis of protein-DNA conjugates was previously described [23,24]. The ADAP methodology is established on the principle of (auto)antibody agglutination to DNA-barcoded proteins. This step included 30 min incubation at 37 °C of 4  $\mu$ l of plasma and 8  $\mu$ l protein-DNA conjugate mixture. Formation of immune complexes positioned compatible DNA conjugates in close proximity. Addition of ligation mixtures enabled ligation of nearby DNA to form complete DNA amplicons. This step in the protocol included 15 min incubation at 30 °C of 116  $\mu$ l ligation solution together with 4  $\mu$ l sample mixture. Next, the protocol included a step with pre-amplification. Mixture of primers and 25  $\mu$ l ligation solution from previous step was followed by 13 PCR cycles (95 °C for 10 min, 95 °C for 15 s, 56 °C for 30 s). The pre-amplified samples were divided in different wells on 384 plate, specific primers to each conjugate were added in each well separately.

SYBR green-based qPCR (RT-qPCR) were used for quantification in 40 cycles (95 °C for 10 min, 95 °C for 30 s, 56 °C for 1 min, 40 cycles) in Roche Lightcycler 480 System II (Roche Diagnostics International AG, Rotkreuz, Switzerland). A strong qPCR signal, represented by a low cycle threshold (Ct), was proportional to a larger count of amplifiable DNA conjugates which in turn were proportional to a larger count of antibody binding interaction to these specific protein-DNA

conjugate. Antibody levels were presented as  $\Delta\text{Ct}$ , defined as the Ct value of the average blank (phosphate-buffered saline and Triton-X) in the run subtracted by the Ct value of the sample. The ADAP SARS-CoV-2 assays were previously used for surveillance by The California Department of Public Health (CDPH) [26].

### Statistical analyses

In this study, participants were divided into three groups T1D, T2D and control individuals. Continuous variables were summarized as medians and interquartile ranges (IQRs), while categorical variables were presented as counts and percentages. The chi-square test was applied to compare categorical variables. The adjusted  $\alpha$ -value of 0.0167 using Bonferroni method was applied for multiple comparisons between any two of the three groups. A two-sided  $p$ -value below the adjusted  $\alpha$ -value was considered as statistically significant.

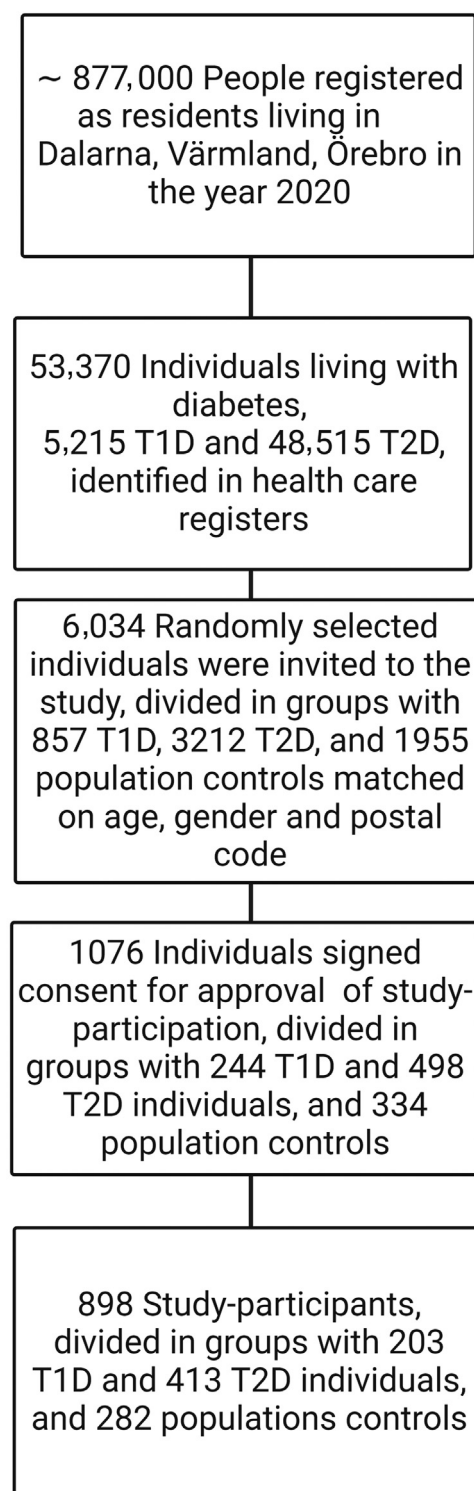
Regression analysis (with non-normality robust standard errors) was performed to examine associations between the groups and BBQ, GAD-7, and MADRS-S scores. Helmert contrast coded variables, c1 and c2, were included to compare diabetes (0.33) vs. controls ( $-0.66$ ); and T1D ( $-0.5$ ) vs. T2D (0.5). For GAD-7 and MADRS-S scores, binary logistic regression models were applied with GAD-7 and MADRS-S scores dichotomized with a cut-off of  $\geq 10$  and  $\geq 20$ , respectively. All regression models adjusted for the following background characteristics of participants: age (continuous), male, high body mass index (BMI) ( $>29.9 \text{ kg/m}^2$ ), and health concerns ( $\geq$  moderate). To explore whether these background characteristics were differently related to the outcome as a function of group (T1D, T2D or controls), we included the interaction terms between these variables and the contrasts; if interactions were non-significant (as evaluated with an omnibus chi-square test or  $F$  test), these terms were excluded from the final model. All regression analyses were run with R statistical software [27], with robust standard errors computed using the *sandwich* package [28]. For regression analysis, a two-sided  $p$ -value below 0.05 was considered as statistically significant.

## Results

### Demographics

The regional health care registers were used to identify a total of 5215 T1D and 48,515 T2D individuals. A total of 180,923 controls from the general population were identified in the Swedish Tax Registry. A simple randomized sampling was conducted to select T1D ( $n = 857$ ) and T2D ( $n = 3212$ ) individuals, and matched general controls ( $n = 1955$ ) (Fig. 1). In total, the study included 898 participants divided in groups with 203 T1D, 413 T2D and 282 controls (Fig. 1). We aimed to include fully matched controls for all T1D and T2D individuals, however, we did not achieve this completely. The number of fully matched diabetes-to-control pairs or trios in the study was 201, with a total inclusion of 416 individuals. The participation rate of the total invited was 17.1 % for controls, 28.5 % for T1D and 15.5 % for T2D. Over 90 % in each group of participants contributed with both questionnaire and blood sample (Table 1). The day of sampling for the different study-groups is illustrated in **Supplementary Figure S1**. The rate of returned and completed questionnaires (range 94.7 %–97.5 %) and blood samples (range 90.0–94.1 %) was not different between T1D, T2D and control individuals.

T2D individuals were less often females than males ( $p^{\text{T1D\_T2D}} = 0.0056$ ), older ( $p^{\text{T1D\_T2D}} < 0.0001$ ,  $p^{\text{T2D\_CTRLS}} < 0.0001$ ), with decreased rate of employment ( $p^{\text{T1D\_T2D}} < 0.0001$ ,  $p^{\text{T2D\_CTRLS}} < 0.0001$ ), had higher BMI ( $p^{\text{T1D\_T2D}} < 0.0001$ ,  $p^{\text{T2D\_CTRLS}} < 0.0001$ ) and lower degree of education ( $p^{\text{T1D\_T2D}} < 0.0001$ ,  $p^{\text{T2D\_CTRLS}} < 0.0001$ , Table 1).



**Fig. 1.** Flow-chart illustration the process of participant assembly. The sample collection period was from February to July 2021. T1D; type 1 diabetes; T2D; type 2 diabetes.

Both T1D and T2D individuals consumed alcohol less often compared to population controls ( $p^{\text{T1D\_CTRLS}} < 0.0001$ ,  $p^{\text{T2D\_CTRLS}} < 0.0001$ ), while there was no statistically significant difference in smoking ( $p^{\text{T1D\_T2D}} = 0.7513$ , Table 1).

The controls reported to be more often married compared to T1D ( $p^{\text{T1D\_CTRLS}} = 0.0055$ ), and population controls reported the lowest rate of cramped housing ( $p^{\text{T1D\_CTRLS}} < 0.0001$ ,  $p^{\text{T2D\_CTRLS}} = 0.0143$ , Table 1).

**Table 1**  
Demographic questionnaire.

N	Type 1 diabetes 203	Type 2 diabetes 413	Population controls 282	p-values
Answered questionnaire,% (n)	97.5 % (198/203)	94.7 % (391/413)	96.8 % (273/282)	$p^{T1D\_T2D} = 0.1415$ , $p^{T1D\_CTRL} = 0.7860$ , $p^{T2D\_CTRL} = 0.1805$ , $p^{T1D\_T2D} = 0.0948$ , $p^{T1D\_CTRL} = 0.3460$ , $p^{T2D\_CTRL} = 0.4278$
Donated blood samples,% (n)	94.1 % (191/203)	90.0 % (372/413)	91.8 % (259/282)	$p^{T1D\_T2D} = 0.0056$ , $p^{T1D\_CTRL} = 0.3766$ , $p^{T2D\_CTRL} = 0.0439$
<b>Gender</b> female,% (n)	51.2 % (104/203)	39.5 % (163/413)	47.2 % (133/282)	$p^{T1D\_T2D} < 0.0001$ , $p^{T1D\_CTRL} < 0.0001$ , $p^{T2D\_CTRL} < 0.0001$
<b>Age</b> years, Median (IQR)	58 (45–69)	70 (63–77)	66 (60–73)	$p^{T1D\_T2D} < 0.0001$ , $p^{T1D\_CTRL} < 0.0001$ , $p^{T2D\_CTRL} < 0.0001$
18–64 years,% (n)	67.5 % (137/203)	29.8 % (123/413)	44.0 % (124/282)	
≥ 65 years,% (n)	32.5 % (66/203)	70.2 % (290/413)	56.0 % (158/282)	
<b>Body Mass Index</b> , Median (IQR) (kg/m <sup>2</sup> )	26.1 (23.3–29.2)	28.1 (25.7–31.4)	26.0 (24.0–28.4)	$p^{T1D\_T2D} < 0.0001$ , $p^{T1D\_CTRL} = 0.1017$ , $p^{T2D\_CTRL} < 0.0001$
< 25.0,% (n)	40.9 % (72/176)	20.7 % (60/290)	37.1 % (86/232)	
25.0–29.9,% (n)	38.1 % (67/176)	44.5 % (129/290)	47.8 % (111/232)	
≥ 30.0,% (n)	21.0 % (37/176)	34.8 % (101/290)	15.1 % (35/232)	
<b>Education</b>				$p^{T1D\_T2D} < 0.0001$ , $p^{T1D\_CTRL} = 0.2779$ , $p^{T2D\_CTRL} < 0.0001$
Elementary School,% (n)	14.2 % (27/190)	33.4 % (125/374)	14.0 % (37/265)	
High School,% (n)	48.4 % (92/190)	41.2 % (154/374)	41.5 % (110/265)	
University,% (n)	37.4 % (71/190)	25.4 % (95/374)	44.5 % (118/265)	
<b>Civil status</b>				$p^{T1D\_T2D} = 0.1250$ , $p^{T1D\_CTRL} = 0.0055$ , $p^{T2D\_CTRL} = 0.1152$
Single (Including Solitaire, Partner, Live apart, Divorced/separated, Widowed),% (n)	49.7 % (98/197)	43.0 % (164/381)	36.9 % (100/271)	
Married,% (n)	50.3 % (99/197)	57.0 % (217/381)	63.1 % (171/271)	
<b>Do you drink alcohol?</b>				$p^{T1D\_T2D} = 0.4018$ , $p^{T1D\_CTRL} < 0.0001$ , $p^{T2D\_CTRL} < 0.0001$
No,% (n)	25.7 % (47/183)	22.4 % (76/339)	10.1 % (26/258)	
Yes,% (n)	74.3 % (136/183)	77.6 % (263/339)	89.9 % (232/258)	
<b>Do you smoke?</b>				$p^{T1D\_T2D} = 0.7513$ , $p^{T1D\_CTRL} = 0.0353$ , $p^{T2D\_CTRL} = 0.0421$
No,% (n)	90.8 % (177/195)	91.6 % (347/379)	95.6 % (261/273)	
Yes,% (n)	9.2 % (18/195)	8.4 % (32/379)	4.4 % (12/273)	
<b>Housing Index*</b>				$p^{T1D\_T2D} = 0.0194$ , $p^{T1D\_CTRL} < 0.0001$ , $p^{T2D\_CTRL} = 0.0143$
< 0.5	30.9 % (58/188)	43.1 % (146/339)	52.9 % (138/261)	
≥ 0.5– 1	56.9 % (107/188)	48.1 % (163/339)	42.9 % (112/261)	
≥ 1	12.2 % (23/188)	8.8 % (30/339)	4.2 % (11/261)	
<b>Occupation</b>				$p^{T1D\_T2D} < 0.0001$ , $p^{T1D\_CTRL} = 0.0013$ , $p^{T2D\_CTRL} < 0.0001$
Student	3.9 % (6/156)	0 % (0/270)	1.0 % (2/210)	
Employed	69.9 % (109/156)	36.7 % (99/270)	54.8 % (115/210)	
Unemployed	1.9 % (3/156)	0.4 % (1/270)	1.4 % (3/210)	
Retired	24.4 % (38/156)	63.0 % (170/270)	42.9 % (90/210)	
<b>Residential area size</b>				$p^{T1D\_T2D} = 0.3271$ , $p^{T1D\_CTRL} = 0.5482$ , $p^{T2D\_CTRL} = 0.0714$
≥ 50,000 residents	43.3 % (88/203)	39.2 % (162/413)	46.1 % (130/282)	
< 50,000 residents	56.7 % (115/203)	60.8 % (251/413)	53.9 % (152/282)	

\* Housing index was computed, as a measure of cramped housing accommodation, by dividing the number people living in the household by the number of rooms in the household. IQR; interquartile range.

‡ Statistical significance level was set as adjusted  $\alpha$ -value = 0.0167.

Self-assessed health was associated with higher scores in T1D and T2D individuals, a sign of poorer health, both in relation to illness and function compared to controls ( $p^{T1D\_CTRLS} < 0.0001$ ,  $p^{T2D\_CTRLS} < 0.0001$ , Table 2).

#### Anxiety, depression, and quality of life

The associations between anxiety (GAD-7), depression (MADRS-S) and quality of life (BBQ) are reported in Table 3. When background characteristics were adjusted for, there were no statistically significant effects of contrasts representing comparisons between diabetes and controls, or between T1D and T2D, in any of the regression models. None of the examined interaction terms between contrasts and background characteristics were statistically significant (all  $p$ -values > 0.1) and these terms were subsequently excluded from the final models (Table 3).

Regardless of group, younger age and reporting health concerns were independently associated with a higher likelihood of having (at

least) moderate levels of anxiety and depression symptoms, as well as a lower quality of life score. Being female was associated with increased likelihood of having moderate levels of anxiety, and having a high BMI ( $\geq 30.0$  kg/m<sup>2</sup>) was associated with a lower quality of life score, irrespective of group (Table 3).

#### SARS-CoV-2 seroprevalence

Self-reported SARS-CoV-2 related demographics including adherence to government guidelines and recommendations, rate of infection, hospital care and vaccination status are presented in **Supplementary Table S1**. The frequency of reported prior COVID-19 infection were 7.1 % in T1D individuals, 4.7 % in T2D individuals and 6.7 % in population controls ( $p^{T1D\_T2D} = 0.2323$ ,  $p^{T1D\_CTRL} = 0.8410$ ,  $p^{T2D\_CTRL} = 0.2539$ ). In total, 6 individuals had been hospitalized before study entry for COVID-19 in the entire cohort, 5 of these individuals were T2D individuals. The self-reported adherence to the recommendations by The Public Health Agency of Sweden were strong



**Table 2**  
Health questionnaire on self-perceived health. .

	Type 1 diabetes	Type 2 diabetes	Population controls	p-value
<b>How do you experience that your health is affected by illness?</b>				$p^{T1D\_T2D} = 0.0035$ , $p^{T1D\_CTRL} < 0.0001$ , $p^{T2D\_CTRL} < 0.0001$
None	5.1 % (10/195)	16.0 % (61/381)	40.8 % (108/265)	
Slightly	27.2 % (53/195)	27.8 % (106/381)	32.1 % (85/265)	
Moderate	45.6 % (89/195)	38.1 % (145/381)	17.4 % (46/265)	
Largely	19.5 % (38/195)	15.2 % (58/381)	8.7 % (23/265)	
Total	2.6 % (5/195)	2.9 % (11/381)	1.1 % (3/265)	
<b>How do you experience the impact on your level of functioning?</b>				$p^{T1D\_T2D} = 0.3521$ , $p^{T1D\_CTRL} < 0.0001$ , $p^{T2D\_CTRL} < 0.0001$
None	17.8 % (35/197)	22.4 % (85/379)	36.0 % (96/267)	
Slightly	36.5 % (72/197)	29.8 % (113/379)	37.5 % (100/267)	
Moderate	31.5 % (62/197)	30.6 % (116/379)	18.0 % (48/267)	
Largely	13.7 % (27/197)	15.8 % (60/379)	8.2 % (22/267)	
Total	0.5 % (1/197)	1.3 % (5/379)	0.4 % (1/267)	

\*Statistical significance level was set as adjusted  $\alpha$ -value = 0.0167.

**Table 3**  
Anxiety, depression, and quality of life questionnaire. Estimates are unstandardized regression coefficients (standard errors) for binary outcomes (MADRS-S, GAD-7) and continuous outcome (BBQ). c1 and c2 are Helmert contrast coded variables to compare diabetes (0.33) vs. controls (−0.66); and T1D (−0.5) vs. T2D (0.5). BMI; body max index, MADRS-S; Montgomery Åsberg Depression Rating Scale, GAD-7; Generalized Anxiety Disorder Assessment, BBQ; Brunnsvikén-Brief Quality of life scale.

Explanatory variables	Outcome variable		
	MADRS-S (≥20)	GAD-7 (≥10)	BBQ
c1: Diabetes vs. controls	−0.29 (0.39)	−0.15 (0.32)	3.46 (1.82)
c2: Type 2 diabetes vs. Type 1 diabetes	0.21 (0.44)	0.22 (0.36)	4.01 (2.24)
Male gender	−0.46 (0.32)	−0.72** (0.27)	0.05 (1.60)
Age (continuous)	−0.03* (0.01)	−0.04*** (0.01)	0.15* (0.07)
BMI high (≥30.0 kg/m <sup>2</sup> )	0.52 (0.33)	0.29 (0.28)	−4.86* (1.96)
Health concern (≥ moderate)	2.07*** (0.46)	1.41*** (0.32)	−13.68*** (1.76)

\*\*\*  $p < 0.001$   
\*\*  $p < 0.01$   
\*  $p < 0.05$

in all groups (97.1–100 %). The frequency of individuals who reported taking a COVID-19 test were increased for T1D individuals (47.2 %) compared to T2D individuals (34.4 %,  $p^{T1D\_T2D} = 0.0027$ ) but not when compared to population controls (40.3 %,  $p^{T1D\_CTRL} = 0.13702$ , **Supplementary Table S1**). The vaccinated individuals in each study group at time of sampling were 10.6 % for T1D, 19.6 % for T2D, and 37.2 % for population controls ( $p^{T1D\_T2D} = 0.0056$ ,  $p^{T1D\_CTRLS} < 0.0001$ ,  $p^{T2D\_CTRLS} < 0.0001$ , **Supplementary Table S1**). Of these individuals, in total 174 study-participants had a blood-sample analyzed for SARS-CoV-2 SC2\_S1 antibodies. The day of vaccination was missing in 4 cases, 4 individuals were NCP positive as an indication of prior infection, and 9 individuals were vaccinated following study-sampling. The antibody response following vaccination for the remaining 157 individuals are illustrated in **Supplementary Figure S2**.

Samples from a total of 217 blood donors, collected in 2014 and 2018 respectively, were analyzed to establish the cut-offs representing 7ΔCt and 3ΔCt, respectively, for SARS-CoV-2 NCP and SC2\_S1 antibodies (**Supplementary Figure S3**). The seroprevalence of SARS-CoV-2 NCP antibodies were 8.9 % for T1D individuals, 3.9 % for T2D individuals and 4.0 % for population controls ( $p^{T1D\_T2D} = 0.0182$ ,  $p^{T1D\_CTRLS} = 0.0261$ ,  $p^{T2D\_CTRLS} = 0.9136$ , **Fig. 2A**). In comparison, the seroprevalence of SARS-CoV-2 SC2\_S1 antibodies were 16.8 % for T1D individuals, 14.0 % for T2D individuals and 25.5 % for population controls ( $p^{T1D\_T2D} = 0.3815$ ,  $p^{T1D\_CTRLS} = 0.0266$ ,  $p^{T2D\_CTRLS} = 0.0003$ , **Fig. 2B**).

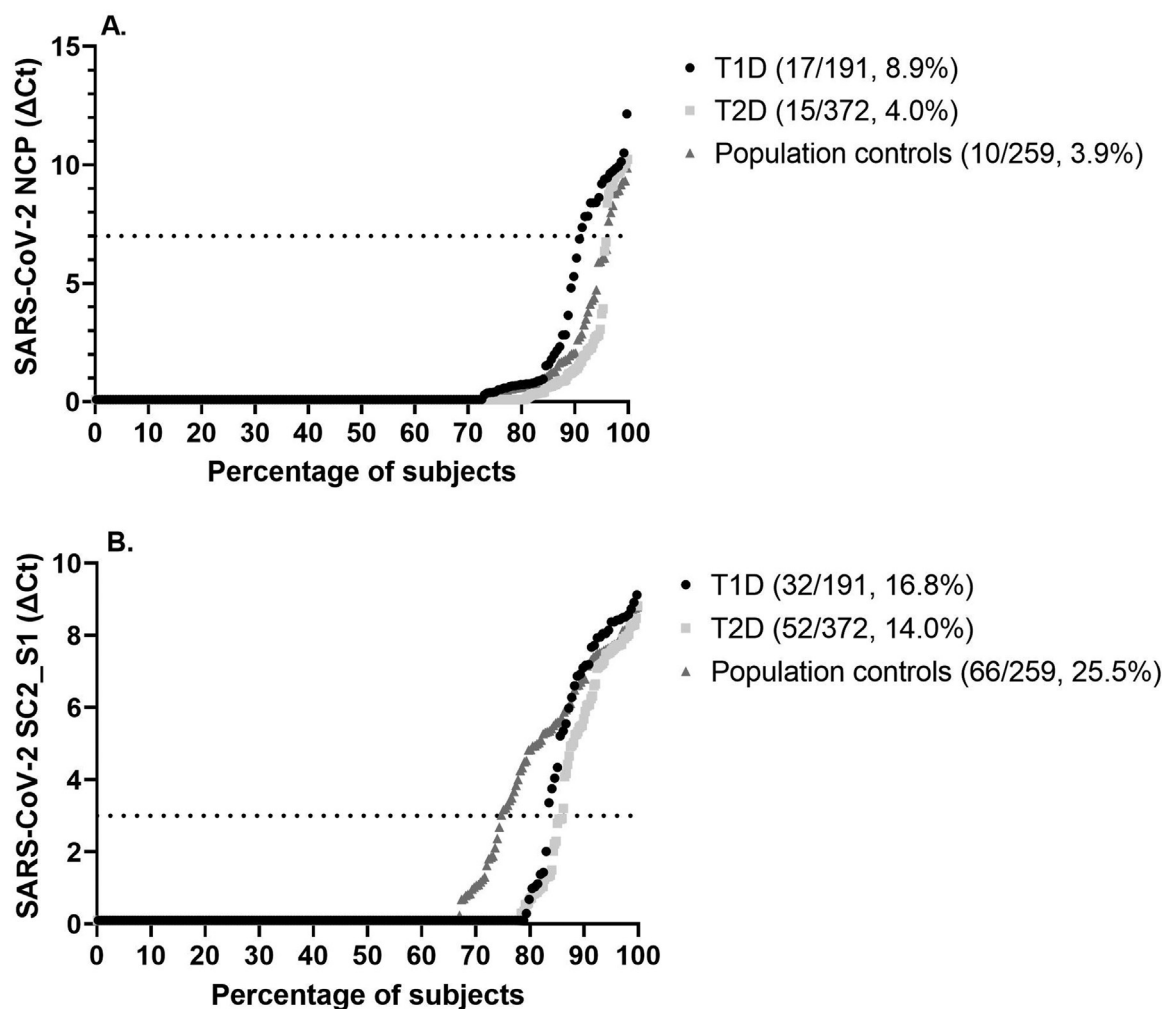
The cumulative incidence of SARS-CoV-2 seroprevalence is illustrated in **Supplementary Figure S4A**. Seroprevalence point estimate per month decreased from February (NCPab-8.25 %, S1ab-15.73 %) to March (NCP-ab- 5.94 %, S1ab-12.17 %). NCPab seroprevalence was thereafter unaltered (April 4.9 %, May/June 5.0 %), while S1ab seroprevalence increased (April 12.7 %, May/June 16.7 %) with increasing number of vaccinated individuals (**Supplementary Figure S4B**).

**Discussion**

In this study we report the following important findings. First, a higher SARS-CoV-2 NCP antibody prevalence was found in T1D compared to T2D and population controls. Second, regardless of study group, anxiety, depression, and decreased quality of life was associated with younger age and with self-reported general health concerns. Third, females showed increased anxiety compared to males while an increased BMI were related to a lower QoL.

Observed demographic differences related to gender and education confirms previous reports [29,30]. A lower employment rate in the T2D individuals was likely explained by an increased number of retired individuals. The decreased self-reported alcohol consumption in both T1D and T2D compared to population controls was unexpected. A previous study found differences between genders with lower intake of alcohol in females. In agreement with our results, the previous study identified a larger group of individuals living with diabetes who did not use alcohol [31]. It should be noted that the controls in our study were invited to match the T1D and T2D cohorts on age as well as gender, and this group does not necessarily represent the demographics of the general public.

Anxiety, depression, and decreased QoL were not related specifically to T1D or T2D but instead associated to demographic variables across the study cohorts. A number of these associations, such as increased mental health problems in females and younger age groups, were previously reported in a larger meta-analysis [32]. It has been recognized during non-pandemic circumstances that both T1D and T2D are chronic diseases associated with an overall lower QoL [33]. Mental health issues have been recognized not only to lower the overall quality of life but also to decrease the ability for disease management [34]. In regard to the COVID-19 pandemic, individuals living with diabetes were reported to have reduced psychosocial health and was associated specifically to disease-related concerns including the risk of severe or fatal illness if infected, complications in diabetes management if infected, as well as the stigma of being classified as a risk group [35]. Female gender and T1D were two factors associated with increased worry and poorer psychosocial health [35]. In Australia, comparing the pre-pandemic with the pandemic period found lower quality of life but no depression or anxiety in T2D



**Fig. 2.** Quantile plots illustrating A, SARS-CoV-2 Nucleocapsid (NCP) and B, Spike (SC2\_S1) antibodies for groups of type 1 diabetes (T1D, black circles) and type 2 diabetes (T2D, light grey squares) subjects, and population controls (dark grey triangles).

during the pandemic [36]. In contrast, similar to our study, depressive symptoms during the pandemic in adults with type 2 diabetes were associated with female gender and obesity and was more than 1.6 times higher during COVID-19 than before the pandemic [37]. A control group was not included in the latter study. Therefore, it cannot be excluded that these effects of the pandemic were present regardless of whether individuals were living with diabetes or not as reported in our study.

Individual living with diabetes were less often married compared to population controls. This was reflected in the housing index where the population controls reported to live less cramped compared to T1D and T2D individuals. The explanation for these results is unclear, however, it may be speculated to be associated with a selection bias related to motivation of participation in population controls compared to T1D and T2D cohorts. Speculatively, in relation to viral exposure, the civil status of being single could either translate into less exposure explained by fewer household contacts, or higher exposure associated with more contacts outside of the household.

A number of different explanations could be suggested to explain the higher NCP seroprevalence in individuals with T1D. First, a higher employment rate compared to individuals with T2D could indicate that the T1D group was more out and about and therefore at increased risk of infection. Second, the increased seroprevalence in individuals with T1D could be explained by living in more crowded homes, as indicated in the housing index in our study. Third, the self-assessed questionnaires indicated comparable infection rates

between individuals with T1D and T2D, it could therefore be speculated that the antibody response to the virus was stronger in T1D subjects.

In this study, data on glucose control was not available, however, HbA1c levels for people living with T1D or T2D were not different on a national level during the pandemic compared to previous years (2016–2022), based on data from the National Diabetes Register (NDR), see (Supplementary Table S2).

The sample collection period was associated with low viral spread and increased vaccine coverage. The difference in vaccination status, with higher rate in population controls, is of interest as it suggests that communicated risk groups might not have been prioritized, or that the risk groups were either skeptical to vaccination or poorly informed. The higher rate of vaccination in population controls explain the conflicting seroprevalence for spike protein compared to NCP antibodies between population control and individuals living with diabetes in our study.

The seroprevalence were lower compared to nationally reported data collected in April 2021 from the Swedish Public Health Agency (PHA) [38]. Our samples were collected February to March 2021 which may explain the lower level of vaccination as compared to the April report from PHA [38]. We suggest that this is associated with differences in investigated areas, from populated cities and rural countryside. At the same time, it should be noted that there were no differences in seroprevalence between rural and city areas including Örebro, Sweden's fifth largest city, with an approximate population

of 150,000 inhabitants (data not shown). The differences seen compared to the data from the Swedish PHA could also be explained by differences in methodology and the fact that the fraction of participants being vaccinated was lower in this study as compared to the report by the Swedish PHA [38]. A nation-wide Swedish study found individuals with T2D but not T1D, compared to the general population, were associated with COVID-19-related comorbidities including hospitalization, need of intensive care and increased mortality [39]. Considering these reports as well as the communicated classification of diabetes as a risk group in Sweden, our study offers important insight by suggesting that these circumstances did not transfer into decreased physical health among individuals living with diabetes. The overall stable HbA1c levels for individuals living with T1D and T2D on a national level (NDR data, not shown), before and during the pandemic, could be seen as indicator to support this assumption.

Strengths of our study include matched invitation of population controls to individuals living with diabetes based on age, gender and place of residence. In addition, we present data from multiple regions, Dalarna, Örebro and Värmland, located in central Sweden. The response rate among participants was high with few missing data points.

A number of limitations should be noted.

First, that the self-reported vaccination status was not confirmed in health registers and second, that we cannot explain the divergence between reported vaccination and measured spike-antibodies. A reason for this may be that the individuals had not passed the first month of the first dose to efficiently build immunity, and they may not have received the second dose to mount strong enough immune response to exceed the cut-off for positivity.

A second limitation was the lack of base-line data prior to the pandemic. This precluded results from being directly related or associated to the ongoing SARS-CoV-2 pandemic. Longitudinal follow-up before and during the pandemic suggested a 3-fold increased prevalence of depression symptoms [40]. Similar longitudinal studies are warranted during and after the pandemic for assessment of long-term complications.

Third, it should be acknowledged that obesity and increased health issues are known to coexist with diabetes, our study does not provide novel findings in these aspects but confirm what was already previously known.

Fourth, since the inclusion rate of participants from the total number of invited individuals was below 30 %, a selection bias could not be excluded. Achievement of the goal of a random selection process could be questioned since approximately 0.1 % (898/877,000) of all residents living in the area were participating in the study.

In conclusion, gender, age, and general health concerns were associated with diminished mental health and lower QoL regardless of whether the individuals had diabetes or not. An increased SARS-CoV-2 infection rate in T1D subjects is speculatively explained by lower age and higher employment rate, causing increased societal viral exposure in this group.

## Author contribution

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published. AL, ÅL and JJ developed the study concept and design, all authors were involved in the interpretation of the data and critically revised, completed and approved the final version of the manuscript. JJ is the guarantor of this work.

## Declaration of competing interest

JJ has received consultant- or lecture fees from Abbot, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Medtronic, Merck Sharp and

Dome, Nordic Infucare, Novo Nordisk, and Sanofi. ÅL is a member of the Scientific Advisory Board of Diamyd Medical. C.T.T. was employed by Enable Biosciences. C.T.T. is a shareholder in Enable Biosciences. C.T.T. is inventor of the ADAP patent licensed from University of California, Berkeley to Enable Biosciences. The ADAP assay used in this study is a product in development. This does not alter our adherence to journal policies on sharing data and materials.

No further conflicts of interest to declare.

## CRediT authorship contribution statement

**Lind Alexander:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Cao Yang:** Formal analysis, Methodology, Software, Writing – review & editing. **Hesser Hugo:** Formal analysis, Methodology, Software, Writing – review & editing. **Hardstedt Maria:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Jansson Stefan:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Lernmark Åke:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – original draft, Resources, Writing – review & editing. **Sundqvist Martin:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Tevell Staffan:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Tsai Cheng-ting:** Funding acquisition, Investigation, Methodology, Validation, Writing – review & editing. **Wahlberg Jeanette:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Jendle Johan:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

## Funding

This work was supported by NIH SBIR 2R44DK110005–02, Strategic Research Area Exodiab Dnr 2009–1039, and the Swedish Foundation for Strategic Research Dnr IRC15–0067.

## Acknowledgments

We thank research assistant Filippa Jendle for data management and the laboratory assistants Zeliha Mestan and Samia Hamdan for administrative management.

## Data sharing and data availability

The data that supports the findings of this study are available in the supplementary material of this article.

## Ethics approval statement

The study protocol was approved (number d-nr 2020–04611) by Swedish Ethical Review Authority and the study was conducted in accordance with International Conference on Harmonization-Good Clinical Practice guidelines.

## Patient consent statement

All participants gave written consent to participate in the study.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.deman.2023.100194.

## References

- [1] Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed* 2020;91(1):157–60.
- [2] Sim K, Huak Chan Y, Chong PN, Chua HC, Wen Soon S. Psychosocial and coping responses within the community health care setting towards a national outbreak of an infectious disease. *J Psychosom Res* 2010;68(2):195–202.
- [3] Van Bortel T, Basnayake A, Wurie F, Jambai M, Koroma AS, Muana AT, et al. Psychosocial effects of an Ebola outbreak at individual, community and international levels. *Bull World Health Organ* 2016;94(3):210–4.
- [4] Rubin GJ, Potts HW, Michie S. The impact of communications about swine flu (influenza A H1N1v) on public responses to the outbreak: results from 36 national telephone surveys in the UK. *Health Technol Assess* 2010;14(34):183–266.
- [5] Dubey S, Biswas P, Ghosh R, Chatterjee S, Dubey MJ, Chatterjee S, et al. Psychosocial impact of COVID-19. *Diabetes Metab Syndr* 2020;14(5):779–88.
- [6] Pierce M, Hope H, Ford T, Hatch S, Hotopf M, John A, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry* 2020;7(10):883–92.
- [7] McGinty EE, Presskreischer R, Han H, Barry CL. Psychological distress and loneliness reported by US adults in 2018 and April 2020. *JAMA* 2020;324(1):93–4.
- [8] Salari N, Hosseini-Far A, Jalali R, Vaisi-Raygani A, Rasoulopoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Global Health* 2020;16(1):57.
- [9] Bäuerle A, Teufel M, Musche V, Weismüller B, Kohler H, Hetkamp M, et al. Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany. *J Public Health (Oxf)* 2020;42(4):672–8.
- [10] Peters A, Rospleszcz S, Greiser KH, Dallavalle M, Berger K. The impact of the COVID-19 pandemic on self-reported health. *Dtsch Arztebl Int* 2020;117(50):861–7.
- [11] Nishiura H, Jung SM, Linton NM, Kinoshita R, Yang Y, Hayashi K, et al. The extent of transmission of novel coronavirus in Wuhan, China, 2020. *J Clin Med* 2020;9(2).
- [12] Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health* 2020;17(5).
- [13] Kumar A, Arora A, Sharma P, Anikindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr* 2020;14(4):535–45.
- [14] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092–7.
- [15] Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007;146(5):317–25.
- [16] Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry* 2016;39:24–31.
- [17] Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the comprehensive psychopathological rating scale. *Acta Psychiatr Scand* 1994;89(1):21–8.
- [18] Svanborg P, Asberg M. A comparison between the beck depression inventory (BDI) and the self-rating version of the Montgomery Åsberg Depression Rating Scale (MADRS). *J Affect Disord* 2001;64(2):203–16.
- [19] Fantino B, Moore N. The self-reported montgomery-åsberg depression rating scale is a useful evaluative tool in major depressive disorder. *BMC Psychiatry* 2009;9:26.
- [20] Lindner P, Frykheden O, Forsström D, Andersson E, Ljótsson B, Hedman E, et al. The Brunnsviken brief quality of life scale (BBQ): development and psychometric evaluation. *Cogn Behav Ther* 2016;45(3):182–95.
- [21] Lind A, de Jesus Cortez F, Ramelius A, Bennet R, Robinson PV, Seftel D, et al. Multiplex agglutination-PCR (ADAP) autoantibody assays compared to radiobinding autoantibodies in type 1 diabetes and celiac disease. *J Immunol Methods* 2022;506:113265.
- [22] Tsai CT, Robinson PV, Spencer CA, Bertozzi CR. Ultrasensitive antibody detection by agglutination-PCR (ADAP). *ACS Cent Sci* 2016;2(3):139–47.
- [23] Karp DG, Cuda D, Tandel D, Danh K, Robinson PV, Seftel D, et al. Sensitive and specific detection of SARS-CoV-2 antibodies using a high-throughput, fully automated liquid-handling robotic system. *SLAS Technol* 2020;25(6):545–52.
- [24] Karp DG, Danh K, Espinoza NF, Seftel D, Robinson PV, Tsai CT. A serological assay to detect SARS-CoV-2 antibodies in at-home collected finger-prick dried blood spots. *Sci Rep* 2020;10(1):20188.
- [25] Cortez FJ, Gebhart D, Robinson PV, Seftel D, Pourmandi N, Owyong J, et al. Sensitive detection of multiple islet autoantibodies in type 1 diabetes using small sample volumes by agglutination-PCR. *PLoS ONE* 2020;15(11):e0242049.
- [26] Mehrotra ML, Lim E, Lamba K, Kamali A, Lai KW, Meza E, et al. CalScope: monitoring severe acute respiratory syndrome Coronavirus 2 seroprevalence from vaccination and prior infection in adults and children in California May 2021–July 2021. *Open Forum Infect Dis* 2022;9(7):ofac246.
- [27] Team R.C. R: a language and environment for statistical computing 2016 [Available from: <https://www.R-project.org>].
- [28] Zeileis A, Köll S, Graham N. Various versatile variances: an object-oriented implementation of clustered covariances in R. *J Stat Softw* 2020;95(1):1–36.
- [29] Nordström A, Hadrévi J, Olsson T, Franks PW, Nordström P. Higher prevalence of Type 2 diabetes in men than in women is associated with differences in visceral fat mass. *J Clin Endocrinol Metab* 2016;101(10):3740–6.
- [30] Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. *Int J Epidemiol* 2011;40(3):804–18.
- [31] Jakobsen ML, Larsen JR, Glümer C, Juel K, Ekholm O, Vilsbøll T, et al. Alcohol consumption among patients with diabetes: a survey-based cross-sectional study of Danish adults with diabetes. *Scand J Public Health* 2016;44(5):517–24.
- [32] Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *J Affect Disord* 2020;277:55–64.
- [33] Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American diabetes association. *Diabetes Care* 2016;39(12):2126–40.
- [34] Fisher L, Polonsky W, Asuni A, Jolly Y, Hessler D. The early impact of the COVID-19 pandemic on adults with type 1 or type 2 diabetes: a national cohort study. *J Diabetes Complicat* 2020;34(12):107748.
- [35] Joensen LE, Madsen KP, Holm L, Nielsen KA, Rod MH, Petersen AA, et al. Diabetes and COVID-19: psychosocial consequences of the COVID-19 pandemic in people with diabetes in Denmark—what characterizes people with high levels of COVID-19-related worries? *Diabet Med* 2020;37(7):1146–54.
- [36] Sacre JW, Holmes-Truscott E, Salim A, Anstey KJ, Drummond GR, Huxley RR, et al. Impact of the COVID-19 pandemic and lockdown restrictions on psychosocial and behavioural outcomes among Australian adults with type 2 diabetes: findings from the PREDICT cohort study. *Diabet Med* 2021;38(9):e14611.
- [37] Chao AM, Wadden TA, Clark JM, Hayden KM, Howard MJ, Johnson KC, et al. Changes in the prevalence of symptoms of depression, loneliness, and insomnia in U.S. Older adults with Type 2 diabetes during the COVID-19 pandemic: the look AHEAD study. *Diabetes Care* 2022;45(1):74–82.
- [38] Beser J, Galanis I, Enkirsch T, Kühlmann Berenzon S, van Straten E, Duracz J, et al. Seroprevalence of SARS-CoV-2 in Sweden, April 26 to May 9, 2021. *Sci Rep* 2022;12(1):10816.
- [39] Rawshani A, Kjölhede EA, Rawshani A, Sattar N, Eeg-Olofsson K, Adiels M, et al. Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: a nationwide retrospective cohort study. *Lancet Reg Health Eur* 2021;4:100105.
- [40] Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. *JAMA Netw Open* 2020;3(9):e2019686.