Cohort profile: EFTER-COVID

a Danish nationwide cohort for assessing the long-term health effects of the COVID-19 pandemic

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BMJ Open

Cohort profile: EFTER-COVID – a Danish nationwide cohort for assessing the long-term health effects of the COVID-19 pandemic

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ABSTRACT

Purpose To follow SARS-CoV-2-infected persons up to 18 months after a positive test in order to assess the burden and nature of post acute symptoms and health problems.

Participants Persons in Denmark above 15 years of age, who were tested positive for SARS-CoV-2 during 1 September 2020 to 21 February 2023 using a RT-PCR test. As a reference group, three test-negative individuals were selected for every two test-positive individuals by matching on test date.

Findings to date In total, 2 427 913 invitations to baseline questionnaires have been sent out and 839 528 baseline questionnaires (34.5%) have been completed. Females, the age group 50–69 years, Danish-born and persons, who had received at least one SARS-CoV-2 vaccination booster dose were more likely to participate. Follow-up questionnaires were sent at 2, 4, 6, 9, 12 and 18 months after the test, with response rates at 42%–54%.

Future plans New participants have been recruited on a daily basis from 1 August 2021 to 23 March 2023. Data collection will continue until the last follow-up questionnaires (at 18 months after test) have been distributed in August 2024.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ EFTER-COVID is one of the largest and longest-running surveys of post acute symptoms and health problems after SARS-CoV-2 infection.
⇒ EFTER-COVID includes a date-matched reference group, allowing estimation of associations between SARS-CoV-2 infection and post acute effects.
⇒ EFTER-COVID includes frequent follow-ups allowing evaluation of symptom duration, and uniform collection of data over a long period, enabling comparisons between periods dominated by different SARS-CoV-2 variants.
⇒ Due to the existence of a unique personal identifier, it is possible to link EFTER-COVID data to data from national registers and conduct hybrid studies.
⇒ The main weakness of the study is the potential existence of bias due to the response rate of 34.5% and increased attrition with each successive follow-up questionnaire.

INTRODUCTION

Soon after the start of the SARS-CoV-2 pandemic, repeated reports of patients with lingering post acute symptoms started to appear.[1 2] A plethora of different possible post acute symptoms were reported,[3] but due to the lack of appropriate control groups,[1 2] it was unclear whether all symptoms were related to infection with SARS-CoV-2, or if some were of other unrelated causes. In the beginning, focus was mainly on patients, who had been hospitalised due to moderate to severe COVID-19;[2 4] however, later the occurrence of post acute symptoms among those with mild disease was also reported.[5]

During spring 2021 when planning of this cohort study was initiated, many questions regarding post acute symptoms were yet unanswered. A wide range of post acute symptoms had been mentioned in surveys conducted among members of Facebook groups for COVID-19 survivors,[6] and while this was a good starting point, it also demonstrated a need for more systematic and less biased data collection. Many of the reported symptoms were very unspecific and some of them (eg, exhaustion, anxiety and depression) could easily be influenced by the pandemic itself and the changes it might have imposed on people's lives, which meant that inclusion of time-matched control groups were crucial in order to understand to which extend the symptoms were directly associated with SARS-CoV-2 infection.

Furthermore, knowledge about duration, prognosis and influence on daily life (eg, in the form of sick leave) was naturally sparse, so setting up frameworks for studying this were needed.

During 2020, Denmark established an extensive test strategy,[7] which resulted in one of the highest per capita test incidences in the world.[8] RT-PCR tests were made available free-of-charge at test centres all over the country. There were no restrictions on test indications, meaning that the tested individuals included persons who experienced symptoms or had been in close contact with infected individuals, as well as persons who had to be tested due to for example, their job, or prior to spending time with vulnerable individuals or attending a social gathering. The results of all RT-PCR tests were recorded in the national COVID-19 surveillance system at Statens Serum Institut.

This mass test strategy in combination with the existence of the nationwide digital mailbox system 'e-Boks', provided to every Danish citizen aged 15 years or older, gave us a unique opportunity to study the burden, nature and duration of post acute symptoms and health problems after COVID-19 in the general adult population, including among persons who were asymptomatic or only suffered from mild disease. By including a date-matched test-negative control group, we were able to control for the level of symptoms in the uninfected population.

Data were collected longitudinally and new participants were invited on a daily basis, which made it possible both to study symptom trajectories and also changes over time, related to force of the pandemic, demographics of the infected, shifts in predominating variants and implementation of vaccination programmes.

In this article, we present the structure of this cohort study, named EFTER-COVID ('after COVID').

COHORT DESCRIPTION

Data collection

Data were collected using web-based questionnaires and were combined with nationwide registry data using the unique person identifier (CPR, central person register) assigned to all individuals residing in Denmark. Data were collected in four different prospective study tracks and a retrospective study track. The retrospective track was included, because the study was not initiated until 16 months after the first person was tested positive for SARS-CoV-2 in Denmark. Participants with test dates up to 12 months prior to the initiation of the study were invited for this track, since this was the time when testing of the general population became more common.

Each of the four prospective tracks had a special focus area, in addition to the core questions included across all tracks (figure 1). The focus areas included physical symptoms (track 1), mental health in the form of anxiety and depression (track 2), cognitive difficulties (track 3) and fatigue and post-exertional malaise (PEM, track 4). The survey design, using different tracks rather than asking all participants the same follow-up questions, was chosen in order to be able to include a large series of questions and was made possible by the substantial number of participants included.

In tracks 1–4, participants were enrolled 1 month after their test date except for a smaller fraction of participants, who received special 2 or 4 months baseline questionnaires during project start-up (7% of those invited in the prospective part of the study). The prospective participants were randomly assigned to a track with a distribution of invitations of 40% for track 1, and 20% for each of tracks 2, 3 and 4. The retrospective track consisted of individuals tested 6, 9 and 12 months before study start (1 August 2021).

After the baseline questionnaire, prospective participants would receive follow-up questionnaires at 2, 4, 6, 9, 12 and 18 months. Subsequent follow-up questionnaires were only sent if the participant had consented to this.

If a participant changed infection status, that is, a test-negative participant tested positive after being enrolled in the study, the sequence of questionnaires would be interrupted, and the participant would restart a new sequence of questionnaires (figure 2). Reinfections were defined as receiving a positive test results more than 60 days after the last positive test result. Participants, who changed status from negative to positive would always be invited to restart, whereas participants who changed status from positive to reinfected, would randomly be selected (50% probability) to either restart or continue in the flow they were already in. Second-time reinfected participants, who had been selected to remain in their flow on first reinfection, would also be selected to remain in their flow on their second reinfection.

Follow-up times in the retrospective track were the same as in the other tracks, that is, at 9 and 12 months if applicable, and last questionnaire at 18 months. The questionnaires in this track only contained the core questions asked in all tracks, since the first questionnaire needed to both contain questions about acute symptoms as well as postacute symptoms at the time of replying to the questionnaire. This information was collected using the full symptom panel of 21 symptoms also used in the other tracks (online supplemental table S1).

Recruitment

Participants eligible for invitation were identified based on data from the nationwide central microbiology database (MiBa), where the results of all SARS-CoV-2 RT-PCR tests conducted in Denmark were registered. The number of PCR-confirmed test-positive individuals varied considerably during the pandemic (online supplemental figure S1). Using the unique personal identifier (the CPR number) in the Danish Civil Registration system, it was possible to link the test results to other registers and send survey invitations to the relevant persons in the national digital communication system, eBoks, where each account is linked to the owners' CPR number. The eBoks system allows for two-way communication between citizens and authorities, and is mandatory to use for all inhabitants in Denmark aged 15 years or older, unless exempted. The system is used by 92% of the relevant age group.[9] Those exempted include groups such as persons with severe

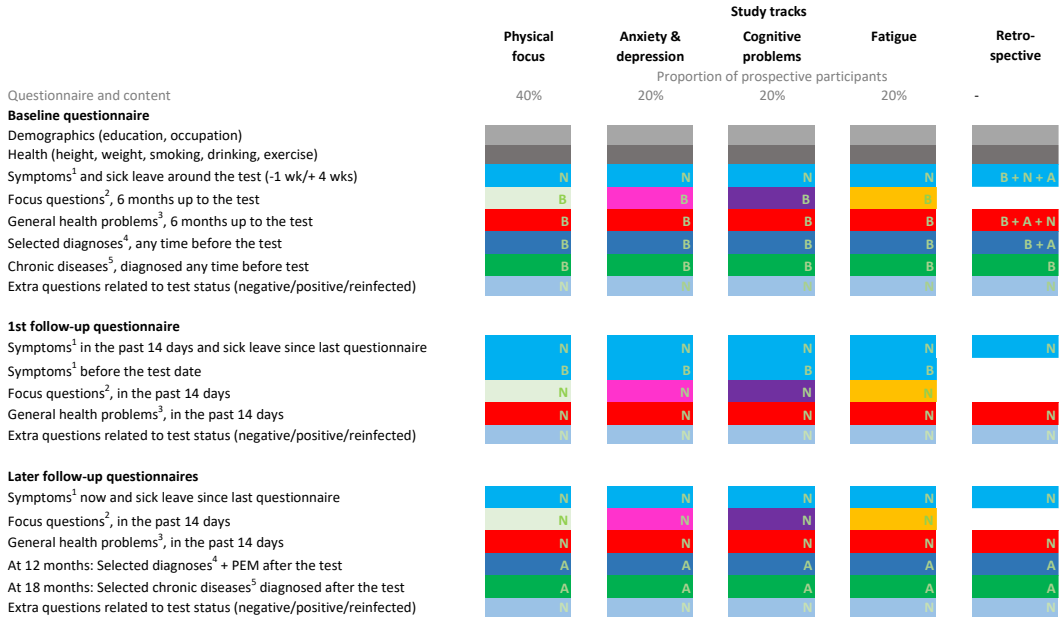

Figure 1 Study tracks and questionnaire content. B, before; N, now; A, after. 1, symptoms, at baseline and before: fever; chills; hot flushes/sweating; headache; muscle or joint pain; fatigue or exhaustion; dizziness; red or watery eyes; runny or stuffy nose; reduced or altered sense of smell; reduced or altered sense of taste; cough; sore throat or pain when swallowing; shortness of breath; chest pain; nausea or vomiting; diarrhoea; abdominal pain; reduced or loss of appetite; reduced arm and leg strength; sleeping or tingling sensation or other abnormal sensations in the legs and arms; other symptoms. Symptoms at follow-up: track 1: same as at baseline, tracks 2–5: fever or chills; reduced or altered sense of taste; reduced or altered sense of smell; shortness of breath; chest pain; muscle or joint pain; fatigue; exhaustion or reduced muscle power; other symptoms. 2, the focus questions consisted of track 1: questions with focus on physical health, track 2: questions with focus on anxiety and depression, adopted from standard questionnaires (full explanation can be found in the 'Questionnaires' subsection of the 'Data Sources' section), track 3: questions from COBRA, Cognitive Complaints in Bipolar Disorder Rating Assessment, track 4: questions from FAS, Fatigue Assessment Scale (FAS, ild care foundation (www.ildcare.nl)) and questions regarding PEM, post-exertional malaise, measured using selected items from the DePaul questionnaire. 3, general health problems: difficulties concentrating; issues with memory; mental exhaustion; physical exhaustion; sleep problems. 4, selected diagnoses: depression; anxiety; PTSD, post-traumatic stress disorder; chronic fatigue syndrome; fibromyalgia. 5, selected chronic diseases: diabetes; asthma; hypertension; COPD or other chronic lung disease; chronic or frequent headaches including migraines; other chronic diseases.

cognitive difficulties, lack of computer access/literacy or no permanent address.

Questionnaires have been sent out on a daily basis since 1 August 2021, and cover SARS-CoV-2 test dates from 1 September 2020 to 21 February 2023, after which we stopped inviting new participants due to planned changes in the Danish testing system. Individuals with test dates from 1 September 2020 to April 2021 were invited to participate in the retrospective track 5, whereas the rest were assigned to one of the prospective tracks 1–4. In general, all individuals who received a positive PCR-test result for the first time were invited. Test-negative individuals with no prior positive test result were invited matched on test-date with a test-negative/test-positive individual ratio of 3:2. However, due to a very high number of participants, who needed to be invited or followed up on, the distribution system capacity was exceeded from 21 February 2022 to 6 September 2022 (ie, in the Omicron period). Therefore, only first-time infected individuals and corresponding controls with test results obtained on a single day of the week (Wednesdays) were invited to participate during this period (online supplemental figure S1), while those with PCR-confirmed reinfections were still invited regardless of the weekday of infection. During 6 September 2022–21 February 2023, we again invited all eligible test-positive individuals and corresponding test-negative controls.

Patient and public involvement

Patients or members of the general public were not involved in planning, recruitment or conduct of the study as such. However, we did include some questions in the questionnaires due to patient advocacy.

Data sources

Questionnaires

The questionnaires were created in SurveyXact (Rambøll, Denmark)[10] and distributed as internet-assessible electronic questionnaires. The questionnaires were available in both Danish and English, and could be filled in using PC, tablet or smartphone.

The baseline questionnaire contained questions regarding acute symptoms (symptoms in the time period 1 week before and until 4 weeks after the test), and

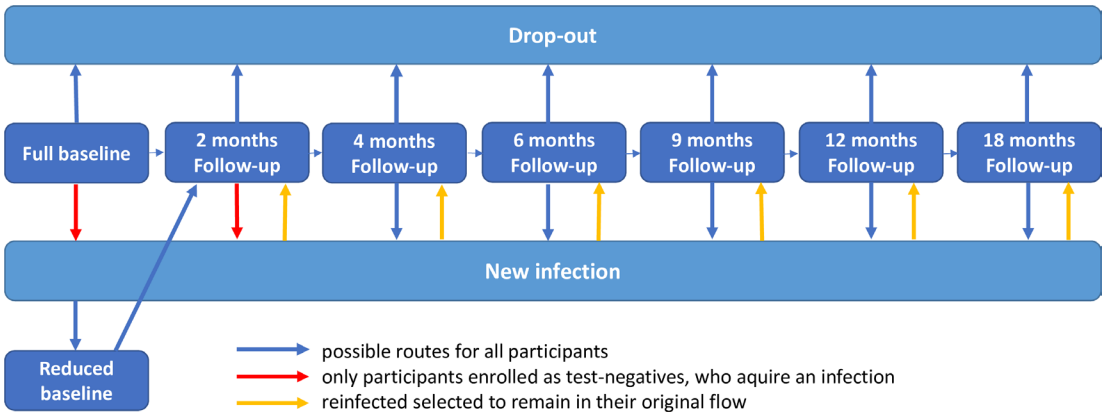

Figure 2 Questionnaire flow. Both test-positive and test-negative individuals selected for participation would receive a full baseline questionnaire 1 month after the test date and proceed with follow-up questionnaires at 2, 4, 6, 9, 12 and 18 months after the test date, unless they dropped out or were infected again. Test-negative participants can restart as test-positive participants with a reduced baseline questionnaire (mainly containing questions regarding symptoms during the acute phase) at any point in time, after which they will continue in the ordinary flow of follow-up questionnaires. Already test-positive participants will at first reinfection be randomly selected to either continue the sequence of questionnaires they had already started or to restart a new sequence beginning with a reduced baseline questionnaire. In case of a second reinfection, individuals, who following their first reinfection were selected to continue in their original flow, will also remain in this flow in case of subsequent reinfections. Colour-coding of arrows: blue, possible routes for all participants; red, only participants enrolled as test-negatives, who acquire an infection; yellow, reinfected selected to remain in their original flow.

additional information such as weight, height, smoking and drinking habits, education, occupation, physical fitness, selected comorbidities and general health conditions and selected disease diagnoses (figure 1, online supplemental table S1).

In addition, each questionnaire contained track specific questions.

Track 1 had an emphasis on physical health. First and foremost, participants in this track were asked about a wider range of physical symptoms at each follow-up than in the other tracks, since the symptom list also included symptoms characteristic of the acute stage of SARS-CoV-2 infection. Additionally, the questionnaires in this track contained selected items from 'the 36-Item Short Form Survey Instrument' (SF-36).[11] The SF-36 covers eight domains, where the questions included in the EFTER-COVID survey include questions from the two domains 'General health perceptions' and 'Role limitations due to physical health'.[12] In addition, there was one question related to change in health. The SF-36 is designed for self-administration to persons aged 14 years and above,[11] which made the questions suitable for inclusion in the EFTER-COVID questionnaires. The full SF-36 questionnaire is widely used for assessing health-related quality of life, and has been translated into at least 120 languages.[13]

Track 2 had an emphasis on mental health, and the participants were asked questions related to anxiety and depression using an existing standard questionnaire. However, during the data collection period, we learnt that this questionnaire was copyright protected. We designed the questionnaire in haste during the pandemic and did not consider that this could be the case. After we became aware of the copyright issue, we immediately reached out to the copyright holders to explain the situation. Unfortunately, it was not possible to arrange a retrospective approval. Consequently, no data related to this questionnaire are available for sharing. Subsequently, these questions were replaced by selected questions from the Generalised Anxiety Disorder (GAD-7)[14] and Patient Health Questionnaire (PHQ-9)[15] questionnaires, for which no permissions are required to reproduce, translate, display or distribute.

Track 3 had an emphasis on cognitive problems and contained questions from the 'Cognitive complaints in bipolar disorder rating assessment' (COBRA) questionnaire.[16] As the name implies, this questionnaire was originally designed for use among patients with psychiatric disorders; however, it has also found use in a 'healthy' reference group.[16] The rating is subjective, but for the original patient group, it has been demonstrated to correlate with social-occupational impairment.[17]

Track 4 had an emphasis on fatigue and post-exertional malaise (PEM) with the inclusion of the 'Fatigue Assessment Scale' questionnaire (FAS, ild care foundation (www.ildcare.nl)[18]) and selected items from the 'DePaul Symptom Questionnaire'.[19] FAS was originally developed for assessment of fatigue among patients with sarcoidosis;[18] however, it has been used for patients with at least 25 other conditions with good validity and reliability.[20] It was therefore considered a suitable tool for assessing fatigue among the EFTER-COVID participants, who might experience an unknown mixture of other symptoms. The DePaul Symptom Questionnaire was originally developed for measuring the degree of PEM among persons with myalgic encephalomyelitis, where this is a key symptom.[19]

The electronic questionnaires were set up so that answers were required for most questions, except questions about height, weight and alcohol consumption in the

baseline questionnaire, which could be left unanswered. Some questions were linked and only asked conditional on the reply to another question. Only questionnaires where all the mandatory questions were answered, were considered completed and eligible for follow-up. The invitations contained contact information for the survey administrators, so invited persons had the possibility to opt out of the survey by contacting us.

Completion of the baseline questionnaire was required for becoming part of the survey. It was possible to skip one follow-up questionnaire and still be invited to fill out the next. If this invitation also received no response, the participant would be defined as having left the cohort and would not receive more questionnaires. In case of no response to an invitation letter, it would be followed by a reminder letter, sent 7–10 days later.

Registry data

The survey responses were supplemented with data originating from several national registers, including the Danish National Patient Register[21] (information on comorbidities used for calculation of Charlson Comorbidity Index scores[22]), the Danish Civil Registration system[23] (information about age, sex and region of residence), the Danish Vaccination Register[24] (dates for each COVID-19 vaccination dose) and the Danish Health Authorisation database (status as healthcare worker). These data were all linked using the CPR number. We defined participants, who had completed a full primary course of vaccination as 'fully vaccinated' (for the most frequently vaccines in Denmark, BNT162b2 (Pfizer) and mRNA-1273 (Moderna) a primary course consisted of two doses).

FINDINGS TO DATE

Response rates and drop-out

Occasionally during the study period, technical problems meant that not all questionnaires were distributed as intended. Participation rates in each follow-up step are based on the numbers of questionnaires that were actually distributed (table 1).

In total, 4 121 752 unique individuals aged 15 year or more had a PCR-test result registered in the nationwide central microbiology database on one of the dates included in the study. Some of these were not eligible for participation due to not having an eBoks either due to age, having died, emigrated or being exempted for other reasons. We sent 2 427 913 invitations to fill-out baseline questionnaires and 839 528 baseline questionnaires (34.5%) have been completed.

Response rates tended to be slightly higher for test-negative than test-positive individuals (table 1A). Response rates for reinfected individuals were higher than for other groups, since only those who had already participated during their first infection were invited again. When comparing response rates for the different study tracks, there were no marked differences (table 1B). The response rates for the follow-up questionnaires were higher than for the baseline questionnaires (table 1C), since these were only sent to those who had already completed the baseline questionnaire and agreed to be contacted again.

As expected, there was a considerable attrition during follow-up with response rates of 42%–54% among those, who received a given follow-up questionnaire (table 1). Response rates for the reinfected individuals were higher, since only those who had responded when invited as first-time test-positives, were invited to participate again. The reasons for non-participation were only known for a small minority of participants, who specifically contacted the administrators to opt out and voluntarily provided this. Among this non-representative minority, some of the most common reasons were other severe diseases or inability to fill-in the questionnaire themselves due to, for example, dementia. However, for the vast majority, we have no information. The response rates and attrition observed in the present study are comparable to what have been observed in some other surveys in Denmark and other Nordic countries.[25–27]

Description of study participants

Based on registry data, it was possible to compare sex, age, vaccination status, occupation in the healthcare sector, residence at nursery homes, country of origin and geographical area of residence for invited persons, who fully or partially completed the baseline questionnaire or did not respond at all (table 2). Compared with the non-responders, those who fully completed the baseline questionnaire were more often females, 50–79 years old, healthcare workers, born in Denmark and had more often received at least one booster dose following initial complete vaccination.

Characteristics of participants at selected timepoints (1, 4 or 12 months after the test of reference) stratified by test status (table 3), indicate that those who replied to a 12 month questionnaire compared with those who had only replied to the 1 month and/or 4 months questionnaire were more likely to be female, 50–69 years old, vaccinated according to the recommendations (ie, have received at least one booster), a healthcare worker, have a medium or long higher education, be in employment or retired, be of Danish origin, living in the capital region, describe their physical activity as 'walk, cycle and light exercise' and their physical form as good or really good, never having smoked or not smoked in the past 5 years.

Based on the calculated Charlson Comorbidity Index scores, those who completed the 12 months questionnaire tended to have higher scores, than those who only completed the 1 month questionnaire.

Table 3 includes all participants at a given point in time, no matter if they filled in the baseline questionnaire or a follow-up questionnaire 12 months after the test. If looking at how many questionnaires each participant has completed (online supplemental table S2), similar patterns are seen for some characteristics, since those

Table 1 Number of completed questionnaires and response rates according to months since the test date, stratified by (A) study track, (B) test status and (C) baseline or follow-up

(A) Stratified by test status					
Month	**Negative**	**Positive**	**First reinfection**	**Second reinfection**	**Total**
1	350 780 (34.3%)	267 725 (32.8%)	14 566 (53.0%)	59 (64.8%)	633 130 (34.0%)
2	95 310 (55.3%)	93 964 (54.6%)	5684 (57.1%)	27 (71.1%)	194 985 (55.2%)
4	109 897 (46.7%)	102 144 (43.0%)	7069 (56.2%)	15 (83.3%)	219 125 (46.0%)
6	99 632 (50.7%)	86 253 (44.1%)	6167 (54.3%)		192 052 (48.4%)
9	136 999 (46.4%)	111 844 (46.2%)	4681 (73.3%)	–	253 524 (46.9%)
12	96 085 (55.9%)	82 801 (56.0%)	2434 (62.7%)	–	181 320 (58.0%)
18	23 024 (56.2%)	19 312 (48.9%)	–	–	42 336 (54.0%)
(B) Stratified by study track					
Month	**Physical health impact**	**Depression and anxiety**	**Cognitive difficulties**	**Fatigue and PEM**	**Retrospective track**
1	266 592 (34.8%)	121 398 (33.1%)	122 583 (33.4%)	122 557 (33.4%)	–
2	85 943 (55.2%)	36 324 (54.4%)	36 489 (55.1%)	36 229 (55.1%)	–
4	95 268 (45.8%)	41 480 (44.7%)	41 567 (44.5%)	40 810 (44.6%)	–
6	74 621 (50.7%)	32 071 (49.7%)	31 644 (48.5%)	31 075 (47.7%)	22 641 (36.9%)
9	59 283 (59.6%)	25 444 (58.2%)	25 101 (57.4%)	24 499 (56.2%)	119 197 (38.1%)
12	44 055 (64.9%)	19 226 (64.6%)	18 713 (63.9%)	18 411 (63.4%)	80 915 (48.2%)
18	3671 (65.7%)	1849 (68.5%)	1744 (66.4%)	1697 (65.4%)	33 375 (49.9%)
(C) Stratified by baseline or follow-up					
	Prospective		**Retrospective**		
Month	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
1	632 130 (33.9%)	–	–	–	
2	15 340 (37.7%)	179 645 (57.3%)	–	–	
4	37 856 (37.0%)	181 269 (47.3%)	–	–	
6	–	169 411 (49.6%)	22 641 (36.9%)	–	
9	–	134 327 (58.3%)	107 324 (36.4%)	11 873 (65.8%)	
12	–	100 405 (64.4%)	24 189 (32.8%)	56 726 (60.3%)	
18	–	8961 (66.3%)	–	33 375 (49.9%)	

The proportion of fully completed questionnaires among all invited persons at a given point in time is indicated in brackets.
Due to the later start especially in track 5, the total number of questionnaires at month one is not equal to the total number of questionnaire flows. If a person changed infection status, that is, from test-negative to test-positive (n=39 085) or from test-positive to reinfected (n=14 536) or second-time reinfected (n=59), this person might have participated in more than one questionnaire flow, and appear more than once in the table. To avoid problems with lack of independence of observations, each participant will usually only be included once in the studies based on EFTER-COVID data.
It was possible to enrol in a prospective track 1, 2 or 4 months after the test, whereas enrolment in the retrospective track took place 6, 9 or 12 months after the test.
PEM, post-exertional malaise.

who had replied to five or more questionnaires were more likely to be 60–89 years old, have received at least one booster, be of Danish origin, retired, have a medium length higher education, be in good physical form and not having smoked within the past 5 years. This group were also more likely to have a Charlson Comorbidity Index score above zero.

Studies to date

To date, the EFTER-COVID cohort data set has been used for five separate studies and more studies are underway. The completed studies have focused on post acute symptoms 6–12 months after infection with SARS-CoV-2,[28] post acute symptoms caused by the Omicron variant,[29] post acute sick leave following infection with SARS-CoV-2[30] and acute symptoms in relation to variant and vaccination status.[31]

The results of these studies indicate that even in the general Danish population, where the majority of infected persons were not hospitalised due to COVID-19, 30% of the infected persons experienced at least one

Table 2 Characteristics of invited individuals, stratified by participation status at baseline

	Completed	Partially completed	No response	
	N=839 528	N=66 698	N=1 521 687	P value
Sex				
Female	511 211 (60.9%)	41 844 (62.7%)	741 686 (48.7%)	<0.001
Male	328 317 (39.1%)	24 854 (37.3%)	780 001 (51.3%)	
Age group (years)				
15–19	36 051 (4.3%)	8154 (12.2%)	180 282 (11.8%)	<0.001
20–29	86 372 (10.3%)	10 789 (16.2%)	356 591 (23.4%)	
30–39	97 168 (11.6%)	9751 (14.6%)	304 577 (20.0%)	
40–49	149 288 (17.8%)	10 901 (16.3%)	283 069 (18.6%)	
50–59	199 608 (23.8%)	11 415 (17.1%)	216 204 (14.2%)	
60–69	161 758 (19.3%)	7829 (11.7%)	104 722 (6.9%)	
70–79	91 266 (10.9%)	5535 (8.3%)	54 823 (3.6%)	
80–89	17 113 (2.0%)	2086 (3.1%)	18 299 (1.2%)	
90+	904 (0.1%)	238 (0.4%)	3120 (0.2%)	
Vaccination status*				
At least one booster	730 586 (87.0%)	48 719 (73.0%)	991 845 (65.2%)	<0.001
Fully vaccinated†	76 192 (9.1%)	11 851 (17.8%)	345 987 (22.7%)	
Not fully vaccinated	32 750 (3.9%)	6128 (9.2%)	183 855 (12.1%)	
Charlson Comorbidity Index Score				
0	741 062 (88.3%)	58 912 (88.3%)	1 398 284 (91.9%)	<0.001
1	58 220 (6.9%)	4679 (7.0%)	78 015 (5.1%)	
≥2	40 246 (4.8%)	3107 (4.7%)	45 388 (3.0%)	
Occupation				
Healthcare worker	79 969 (9.5%)	4737 (7.1%)	96 220 (6.3%)	<0.001
Non-healthcare worker	759 559 (90.5%)	61 961 (92.9%)	1 425 467 (93.7%)	
Nursing home				
No	838 597 (99.9%)	66 367 (99.5%)	1 512 601 (99.4%)	<0.001
Yes	931 (0.1%)	331 (0.5%)	9086 (0.6%)	
Origin				
Danish	758 058 (90.3%)	54 673 (82.0%)	1 220 004 (80.2%)	<0.001
Born abroad	72 420 (8.6%)	10 052 (15.1%)	241 183 (15.8%)	
Immigrant	9050 (1.1%)	1973 (3.0%)	60 500 (4.0%)	
Region				
Capital	285 100 (34.0%)	23 036 (34.5%)	547 655 (36.0%)	<0.001
Central Denmark	180 514 (21.5%)	14 283 (21.4%)	327 668 (21.5%)	
Northern Jutland	79 650 (9.5%)	6686 (10.0%)	142 649 (9.4%)	
Zealand	121 360 (14.5%)	9377 (14.1%)	205 400 (13.5%)	
Southern Denmark	172 582 (20.6%)	13 285 (19.9%)	297 042 (19.5%)	
Missing	322 (0.0%)	31 (0.0%)	1273 (0.1%)	

P values were estimated using Student's t-test for continuous variables and Pearson's χ^2 test for categorical variables. No adjustments for multiple comparisons were made. If a person changed infection status, that is, from test-negative to test-positive (n=39 085) or from test-positive to reinfected (n=14 536) or second time reinfected (n=59), this person might have participated in more than one questionnaire flow, and appear more than once in the table. To avoid problems with lack of independence of observations, each participant will usually only be included once in the studies based on EFTER-COVID data.

*Vaccination status 14 days prior to the test causing the individual to be invited to participate in the study.

†Participants were defined as 'fully vaccinated', when they had completed a full primary course of vaccination (for the most frequently vaccines in Denmark, BNT162b2 (Pfizer) and mRNA-1273 (Moderna), a primary course consisted of two doses).

Table 3 Characteristics of participants, who completed the 1, 4 and 12 months questionnaires

	1 month	4 months	12 months	
	N=632 260	N=219 125	N=181 316	P value
Sex				
Female	385 332 (60.9%)	130 893 (59.7%)	107 592 (59.3%)	<0.001
Male	246 928 (39.1%)	88 232 (40.3%)	73 724 (40.7%)	
Age group				
15–19	28 494 (4.5%)	4710 (2.1%)	3031 (1.7%)	<0.001
20–29	61 734 (9.8%)	14 262 (6.5%)	10 766 (5.9%)	
30–39	72 399 (11.5%)	18 600 (8.5%)	13 430 (7.4%)	
40–49	111 052 (17.6%)	35 015 (16.0%)	28 449 (15.7%)	
50–59	146 417 (23.2%)	55 585 (25.4%)	48 754 (26.9%)	
60–69	123 637 (19.6%)	53 581 (24.5%)	46 598 (25.7%)	
70–79	73 896 (11.7%)	31 958 (14.6%)	25 943 (14.3%)	
80–89	13 896 (2.2%)	5227 (2.4%)	4197 (2.3%)	
90+	735 (0.1%)	187 (0.1%)	148 (0.1%)	
Vaccination*				
At least one booster	546 893 (86.5%)	200 084 (91.3%)	169 120 (93.3%)	<0.001
Fully vaccinated†	59 103 (9.3%)	12 963 (5.9%)	8221 (4.5%)	
Not fully vaccinated	26 264 (4.2%)	6078 (2.8%)	3975 (2.2%)	
Charlson Comorbidity Index Score				
0	556 630 (88.0%)	190 780 (87.1%)	157 618 (86.9%)	<0.001
1	44 649 (7.1%)	16 691 (7.6%)	13 729 (7.6%)	
≥2	30 981 (4.9%)	11 654 (5.3%)	9969 (5.5%)	
Occupation				
Healthcare worker	56 106 (8.9%)	18 719 (8.5%)	19 263 (10.6%)	<0.001
Non-healthcare worker	576 154 (91.1%)	200 406 (91.5%)	162 053 (89.4%)	
Nursing home				
No	631 514 (99.9%)	219 054 (100.0%)	181 246 (100.0%)	<0.001
Yes	746 (0.1%)	71 (0.0%)	70 (0.0%)	
Origin				
Danish	572 575 (90.6%)	203 048 (92.7%)	168 252 (92.8%)	<0.001
Born abroad	53 236 (8.4%)	14 661 (6.7%)	11 877 (6.6%)	
Immigrant	6449 (1.0%)	1416 (0.6%)	1187 (0.7%)	
Region				
Capital	210 708 (33.3%)	73 687 (33.6%)	64 369 (35.5%)	<0.001
Central Denmark	137 851 (21.8%)	46 508 (21.2%)	37 181 (20.5%)	
Northern Jutland	58 765 (9.3%)	20 269 (9.3%)	16 814 (9.3%)	
Zealand	91 903 (14.5%)	32 894 (15.0%)	26 939 (14.9%)	
Southern Denmark	132 806 (21.0%)	45 695 (20.9%)	35 938 (19.8%)	
Missing	227 (0.0%)	72 (0.0%)	75 (0.0%)	
Education				
Primary school (9th–10th grade)	62 203 (9.8%)	16 992 (7.8%)	13 973 (7.7%)	<0.001
Secondary (general/vocational)	52 954 (8.4%)	15 025 (6.9%)	12 261 (6.8%)	
Vocational training	103 368 (16.3%)	36 013 (16.4%)	31 707 (17.5%)	
Higher (1–2 years, vocational academy)	62 520 (9.9%)	21 970 (10.0%)	19 185 (10.6%)	
Higher (2–4 years, BSc)	175 540 (27.8%)	62 861 (28.7%)	57 977 (32.0%)	

Continued

Table 3 Continued

	1 month	4 months	12 months	
	N=632 260	N=219 125	N=181 316	P value
Higher (5 years or more, MSc, PhD)	100 190 (15.8%)	35 247 (16.1%)	30 710 (16.9%)	
Do not know	20 495 (3.2%)	4763 (2.2%)	4105 (2.3%)	
Missing	54 990 (8.7%)	26 254 (12.0%)	11 398 (6.3%)	
Employment				
Employed full-time	277 971 (44.0%)	90 287 (41.2%)	81 133 (44.7%)	<0.001
Employed part-time	50 434 (8.0%)	15 971 (7.3%)	15 549 (8.6%)	
Self-employed	29 925 (4.7%)	9802 (4.5%)	8897 (4.9%)	
Student	46 750 (7.4%)	9596 (4.4%)	7402 (4.1%)	
Pensioner or early retiree	130 519 (20.6%)	54 364 (24.8%)	46 524 (25.7%)	
Stay-at-home parent or on parental leave	5440 (0.9%)	1391 (0.6%)	1023 (0.6%)	
Long-term sick leave	5893 (0.9%)	1813 (0.8%)	1370 (0.8%)	
Unemployed or seeking job	7837 (1.2%)	2486 (1.1%)	1997 (1.1%)	
Benefit recipient	1909 (0.3%)	493 (0.2%)	342 (0.2%)	
Other	20 599 (3.3%)	6668 (3.0%)	5680 (3.1%)	
Missing	54 983 (8.7%)	26 254 (12.0%)	11 399 (6.3%)	
Physical activity				
Hard training or competitive sports[1]	19 477 (3.1%)	4969 (2.3%)	4365 (2.4%)	<0.001
Work out or do gardening[2]	114 163 (18.1%)	39 288 (17.9%)	36 534 (20.1%)	
Walk, cycle or light exercise[2]	358 539 (56.7%)	124 577 (56.9%)	110 238 (60.8%)	
Read, watch TV or similar	85 530 (13.5%)	24 229 (11.1%)	18 917 (10.4%)	
Missing	54 551 (8.6%)	26 062 (11.9%)	11 262 (6.2%)	
Physical form				
Really good	29 919 (4.7%)	10 457 (4.8%)	10 235 (5.6%)	<0.001
Good	206 588 (32.7%)	73 606 (33.6%)	67 984 (37.5%)	
Fair	230 879 (36.5%)	74 941 (34.2%)	64 661 (35.7%)	
Less good	87 190 (13.8%)	27 280 (12.4%)	21 908 (12.1%)	
Poor	23 134 (3.7%)	6780 (3.1%)	5268 (2.9%)	
Missing	54 550 (8.6%)	26 061 (11.9%)	11 260 (6.2%)	
Smoking				
Never	284 011 (44.9%)	94 479 (43.1%)	82 518 (45.5%)	<0.001
Not in the past 5 years	155 826 (24.6%)	58 875 (26.9%)	53 802 (29.7%)	
Yes, within the past 5 years	28 872 (4.6%)	8759 (4.0%)	7665 (4.2%)	
Daily (less than 10 cigarettes/day)	30 305 (4.8%)	8944 (4.1%)	7488 (4.1%)	
Daily (more than 10 cigarettes/day)	28 654 (4.5%)	8765 (4.0%)	7196 (4.0%)	
E-cigarettes/vaping	7564 (1.2%)	2226 (1.0%)	1896 (1.0%)	
Missing	97 028 (15.3%)	37 077 (16.9%)	20 751 (11.4%)	

1, several times/week, 2, at least four times/week. P values were estimated using Student's t-test for continuous variables and Pearson's χ^2 test for categorical variables. No adjustments for multiple comparisons were made. Due to the later start especially in track 5, the total number of questionnaires at month 1 is not equal to the total number of participants. The same individual can be included in all three categories, if the person completed all three questionnaires. If a person changed infection status, that is, from test-negative to test-positive (n=39 085) or from test-positive to reinfected (n=14 536) or second time reinfected (n=59), the person might have participated in more than one questionnaire flow, and appear more than once in the table. To avoid problems with lack of independence of observations, each participant will usually only be included once in the studies based on EFTER-COVID data.
*Vaccination status 14 days prior to the test causing the individual to be invited to participate in the study.
†Participants were defined as 'fully vaccinated', when they had completed a full primary course of vaccination (for the most frequently vaccines in Denmark, BNT162b2 (Pfizer) and mRNA-1273 (Moderna), a primary course consisted of two doses).

symptom from the list (online supplemental table S1) 6–12 months after infection compared with 13% among the non-infected.[28] Emergence of the Omicron variant in Denmark led to a dramatic increase in the number of infected individuals, but reassuringly the occurrence of postacute symptoms was lower than following infection with the Delta variant.[29] Altered sense of smell and taste were reported by 6% and 8%, respectively, 4 months after infection with an Omicron variant, compared with 19% and 24%, following infection with the Delta variant.[29] Compared with those infected with the Delta variant, Omicron infected individuals less often reported fatigue, dyspnoea and cognitive difficulties.[29] Substantial sick leave (more than 4 weeks) during the first 8 months following the acute phase was reported by 4.5% of test-positive participants, compared with 1.4% among test-negative participants.[30] Females, older and obese participants reported substantial sick leave more often than males, younger and normal weight participants.[30] Additionally, chronic disease status was associated with more self-reported sick leave.[30] The pattern of self-reported symptoms during the acute phase were affected by variant and vaccination; most notably, individuals infected during the Omicron period less often reported altered sense of smell and taste.[31]

In summary, the EFTER-COVID project provided a unique opportunity for conducting a range of different studies in relation to health of the Danish population during the pandemic. Publication of new studies based on EFTER-COVID data will be announced at the EFTER-COVID webpage (https://covid19.ssi.dk/overvagningsdata/undersoegelser/efter-covid).

STRENGTHS AND LIMITATIONS

The main strengths of EFTER-COVID are as follows: (1) the size of the study population, where invitation of more than half of the Danish population was made possible by the large number of tests performed (49% of the population of 15 years or above of 4 985 196 individuals per 1 January 2023 were invited[32]), (2) a baseline participation rate (34.5%) equal to what has been possible in previous large questionnaire studies in Denmark[25] and (3) the inclusion of a comparison group of test-negative individuals. Other strengths include the many time points of follow-up, and the fact that data were collected in the same way during periods where different variants were predominant. This was all made possible by the central electronic registration of health and vital data for study participants and the possibility to contact potential participants electronically.

The main weaknesses of EFTER-COVID are the response rate, the attrition at each successive follow-up questionnaire and the risk of bias, which might follow from that. It could be anticipated that persons with no long-term symptoms might be less likely to respond to the questionnaire, however response rates among test-positive and test-negative participants were very similar, so participants without post acute symptoms were also willing to participate, which improves the validity of relative findings in EFTER-COVID. On the other hand, those most affected by cognitive difficulties and/or fatigue, might not have the resources to participate in the study and the prevalence of severe long-COVID might thus be underestimated.

Only citizens who have been PCR-tested for SARS-CoV-2 at least once could be invited to participate in the survey. The more frequently a person was tested, the greater chance of being selected, so bias due to differences in testing behaviour in the Danish population cannot be ruled out. However, since close to half of the population was invited to participate, the invited group will comprise persons with different test frequencies.

FUTURE PLANS

Invitation of new participants stopped on 23 March 2023 (last test date included: 21 February 2023), due to changes in the Danish test strategy, which meant that the so-called community PCR-test track to which citizens could self-refer was discontinued. However, we are still following up on enrolled participants, and are planning to do so until August 2024, when 18 months since the test date have elapsed for all participants. In the future, the current set-up with automatic selection of participants from the microbiology database followed by automated distribution of questionnaires, may also be reused in relation to other infectious diseases.

COLLABORATION

We invite other research groups to collaborate with us on studies where combination of EFTER-COVID data with other data sets can yield new insights for the benefit of the society.

The data sets used in the study comprise individual-level sensitive information from completed questionnaires and national register data. According to the Danish data protection legislation, the EFTER-COVID study group are not allowed to share these sensitive data directly upon request. However, these data are available for research upon reasonable request to The Danish Health Data Authority (register-data, e-mail: kontakt@sundhedsdata.dk) and Statens Serum Institut (questionnaire data, e-mail: aii@ssi.dk) and within the framework of the Danish data protection legislation and required permissions from the relevant authorities.

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Contributors The study was designed and initiated by PB, SE, AH, NMN, AK and AS. The questionnaires were designed by AS, PB, NMN, AK and SE. Collection of data including programming related to this: AS and PB. Data analysis was done by AS and LS. The first draft was written by AS. All authors have critically revised the manuscript and approved the final version. The corresponding author confirms that all listed authors meet authorship criteria and that no one meeting the criteria has been omitted. AS is the guarantor of the study, had access to the data, and controlled the decision to publish and accepts full responsibility for the conduct and content of the study.

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Patient consent for publication Not applicable.

Ethics approval The study involves human participants. This article has been prepared on the basis of a study carried out as part of a task imposed on the Statens Serum Institut according to national legislation. Therefore, no approval requirements from the ethics committees are obliged.The publication only contains aggregated results and no personal data. The publication is therefore not covered by the European General Data Protection Regulation. The EFTER-COVID project was approved by the Danish Governmental law firm ('Kammeradvokaten') and SSI's Compliance Department ('Data protection and Information Security') and is fully compliant with all legal, ethical and IT-security requirements. There are no further approval procedures regarding such studies in Denmark. Participation in the study was voluntary. The invitation letter to participants contained information about their rights under the Danish General Data Protection Regulation (rights to access data, rectification, deletion, restriction of processing and objection) and the type of information about them which might be processed (including registry data). Accessing and filling out the questionnaire after receiving the above information was considered informed consent from the participant's side. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. According to the Danish data protection legislation, the authors are not allowed to share these sensitive data directly upon request. However, the data are available for research upon reasonable request to The Danish Health Data Authority (register-data, e-mail: kontakt@sundhedsdata.dk) and Statens Serum Institut (questionnaire data, e-mail: aii@ssi.dk) within the framework of the Danish data protection legislation and any required permissions from the relevant authorities.

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