Supplement 1

Cod Liver Oil for COVID-19 Prevention (CLOC) Study –

Study protocol, and data analysis plan

The CLOCK investigators

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This supplement contains the following documents:

- A brief introduction to this document
- The first version of the protocol
- Newest amended protocol
- Signed statistical analysis plan

A brief introduction to this document

The document contains the original protocol registered at ClinicalTrials.gov before inclusion in the study was opened, and the newest version with all amendments last registered at ClinicalTrials.gov.

The statistical analysis plan was written and submitted to ClinicalTrials.gov before unblinding of the study on December 13, 2021, and is included in this supplement.

Protocol for the Cod Liver Oil for Covid-19 Prevention Study

Contents

Title

A randomized, parallel-group treatment, participant, investigator, care provider and outcomes assessor masked, two-arm study to assess the effectiveness of cod liver oil compared to placebo in the prevention of Covid-19 and airway infections in healthy adults

Short: Cod Liver Oil for Covid-19 Prevention Study

Shorter: Transtudien

Sponsor and contact details

Sponsor:

Oslo University Hospital, PB 4959 Nydalen, 0424, Oslo

Principal Investigator (PI):

Arne Søraas, MD, PhD
Oslo University Hospital, Department of Microbiology, Section of Research
PB 4959 Nydalen, 0424, Oslo
Email: arne.vasli.lund.soraas@rr-research.no
Phone: +47 90652904

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
1.0: First complete REK approved protocol.	*Completed October 5. Approved October 12, 2020*
1.01:	Completed October 22, 2020
1.02	*Completed October 27. 2020*

Amendment 1 (October 22, 2020)

Use of antigen tests added as these have a very high specificity [18].
Change of full study title: addition of randomized, placebo and airway infections.

Follow up period for definition of serious Covid-19 disease changed from 8 to 4 weeks.

Amendment 2 (October 27, 2020)

Norwegian label translated.
Endpoints described according to ClinicalTrials standard
Endpoints at 12 months moved from secondary endpoints to exploratory endpoints.

1. Protocol Summary

Preliminary evidence from literature and an ongoing study in our lab suggests that cod liver oil may prevent Covid-19 and complications of Covid-19. We will investigate whether this is actually the case or in "Transtudien" by randomizing volunteers to take cod liver oil or placebo (corn oil) during the winter months of 2020-2021.

Schema

June-September 2020: Study design and approvals phase
September-October 2020: Screening and inclusion of participants
October 2020-April 2021: Cod liver oil or placebo taking period
November 2020-April 2021: Obtain registry data
May 2021: Compiling data and publish results
November 2021: End of follow up
2030: End of study.

2035 Destruction of patient list.

2. Introduction

Study Rationale and background

Cod liver oil is an important source of long-chain omega-3 polyunsaturated fatty acids (n-3 LCPUFA), in particular, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), and vitamin D. It is an important supplement for people who do not eat fatty fish as recommended by the Norwegian authorities. The health benefits of EPA and DHA are well documented, indicating protective effects on cardiovascular disease (CVD) and the immune system [1-4]
Vitamin D acts on nuclear receptors on multiple locations and have a wide range of short- and long term effects, including the prevention of rickets, asthma exacerbations [5], and importantly acute respiratory tract infections [6, 7].
The health effects of a combination of polyunsaturated fatty acids with and without vitamin D have recently been investigated in the VITAL study, which included 25,000 participants over five years. No serious safety concerns were noted, although all-cause mortality remained unchanged [4, 8].

In a recent report from Ernæringsrådet (2018), a Norwegian government agency, it was found that low levels of vitamin D were prevalent in the Norwegian population, and it was recommended that all dairy products and plant-based substitutes should be fortified with vitamin D. Cod liver oil is mentioned in Norwegian official dietary advice as an important source of n-3 LCPUFA.

In the Cod Liver Oil for Covid-19 Prevention study (CLOC), 80.000 participants will be randomized to cod liver oil or placebo, aiming to prevent Covid-19 and its complications.

The study is initiated by Oslo University Hospital and is a collaboration with the University of Oslo, the National Institute of Public Health and is partially financed by Orkla Health.

Cod Liver Oil

Fish oils or fat fish are important sources of vitamin D and n-3 LCPUFA in the diet. Cod liver oil contains 10 ug of vitamin D and 1 g of polyunsaturated fatty acids (DHEA 0,6g and EPA 0,4g) per 5 ml and covers the daily requirements for these nutrients with a low risk of overdosing and with a safety profile established through more than 100 years of use. The supplement is widely used in Norway and abroad, and more than 5 million bottles of "Møllers tran", a widely used brand, are produced each year.

The health effects of cod liver oil have been investigated before, including in a randomized controlled study in Norway [9]. However, to our knowledge, no extensive safety studies have been conducted on cod liver oil. Also, most studies are done on either vitamin D or n-3 LCPUFA, and the health effects of the widely used supplement cod liver oil compared to each of these constituents have, to our knowledge, not been described in randomized studies.

Covid-19

Covid-19, the disease caused by the pandemic SARS-CoV-2 virus in 2020, has infected more than 14 million people worldwide and killed more than 0.6 million (Worlometers.info, July 18, 2020).
The most common cause of death is respiratory failure, and most hospitalized patients need extra oxygen supply, and some need mechanical respiratory support in intensive care units. A prominent hypothesis for the pathophysiology of the SARS-CoV-2 virus is that overreaction from the immune system against the virus – a cytokine storm – is involved in causing the lung damage and the life-threatening complications of the disease [10, 11].

Cod liver oil in Covid-19

Vitamin D supplement has been shown to prevent asthma exacerbations and respiratory tract infections [5, 6]. In particular, people with low levels of vitamin D before supplementation benefited. Furthermore, Vitamin D deficiency has been associated with severe disease outcomes and death in Covid-19, and several studies are investigating the use of vitamin D to prevent these outcomes in Covid-19 [12-14](ClinicalTrials.org).
However, not all studies on vitamin D and Covid-19 are positive, and a large UK biobank study found no association between vitamin D levels ten years ago and Covid-19[15].
Omega 3 long-chain fatty acids have immunomodulatory effects and have been shown to be possibly beneficial when given to patients with respiratory support in intensive care units[16].
The safety of the low doses of vitamin D and n-3 LCPUFA in cod liver oil has been proven in multiple studies [4, 8, 9].

Thus, current literature support that the low levels of vitamin D found in cod liver oil may be sufficient to mediate a protective effect against respiratory tract infections. However, this has not been shown in randomized studies on Covid-19, and the evidence is not unambiguous.
Literature also supports that n-3 LCPUFA may have some additional benefits in respiratory infections and that cod liver oil has an excellent safety profile.

Koronastudien

In Koronastudien, 140.000 participants have answered a questionnaire about their use of dietary supplements, demographics, airway symptoms, and risk factors for Covid-19.
In univariate analyses, we have found that participants using vitamin D and or cod liver oil were associated with a reduced risk of Covid-19 (OR 0.8, $p<0.001$) and of serious (hospitalized) Covid-19 with hospitalization (OR 0.3, $p=0.07$).

These protective effects are also seen in preliminary analyses of cod liver oil alone when age, gender, and contact with Covid-19 patients are included in the analyses (OR 0.6, p=0.02) for Covid-19 disease with dyspnea and OR 0.1, p=0.03 for hospitalized Covid-19 disease.

Other short-term health effects of cod liver oil

Cod liver oil and the major constituents, vitamin D and n-3 LCPUFA, have been investigated for a long list of conditions over many years. They have been found to be safe, but many studies have been underpowered to detect smaller effects on health and many need to be validated in new datasets. Our study will not be powered to make conclusions on health effects of cod liver oil, but as exploratory endpoints validating existing findings the randomized data obtained will be of great value both at the end of the cod liver oil taking period and for up to two years which is the follow up period of the study.

In total, 70 Cochrane reviews includes vitamin D and 48 includes omega 3. The most relevant research questions for the CLOC study are:

Intervention	**Cochrane conclusion**	**CLOC study relevancy**
Omega 3-dementia	Considering this and the fact that omega-3 PUFA cannot be synthesised by humans, omega-3 PUFAs might be a promising treatment option for dementia.	Incidence of new dementia in cod liver oil group.
PUFA (including Omega 3)-primary and secondary prevention of cardiovascular disease	Increasing PUFA intake …probably slightly reduces risk of coronary heart disease events from 14.2% to 12.3% (RR 0.87, 95% CI 0.72 to 1.06, 15 trials, 10,076 participants) Increasing PUFA intake probably slightly reduces risk of coronary heart disease and cardiovascular disease events, may slightly reduce risk of coronary heart disease mortality and stroke (though not ruling out harms), but has little or no effect on all-cause or cardiovascular disease mortality.	Incidence of cardiovascular diseases in cod liver oil group.
Vitamin D-cancer prevention	There is currently no firm evidence that vitamin D supplementation decreases or increases cancer occurrence… Vitamin D_3 supplementation decreased cancer mortality and vitamin D supplementation decreased all-cause mortality, but these estimates are at risk of type I errors due to the fact that too few participants were examined, and to risks of attrition bias originating from substantial dropout of participants.	Incidence of new cancer diagnoses in the cod liver oil group.
Vitamin D-all-cause mortality	Vitamin D3 seemed to decrease ….. Because of risks of attrition bias originating from substantial dropout of participants and of outcome reporting bias due to a number of trials not reporting on mortality, as well as a number of other weaknesses in our evidence, further placebo-controlled randomised trials seem warranted.	Does the low dose of vitamin D in cod liver oil reduce mortality?
Vitamin D-fractures	There is high quality evidence that vitamin D plus calcium is associated with a statistically significant	Other fractures was not prevented,

	reduction in incidence of new non-vertebral fractures. However, there is only moderate quality evidence of an absence of a statistically significant preventive effect on clinical vertebral fractures.	but no large studies on cod liver oil exist (Meyer et al 1999)
Vitamin D-dementia	One trial with 4143 participants compared vitamin D3 (400 IU/day) and calcium supplements to placebo. We found low- to moderate-certainty evidence of no effect of vitamin D3 and calcium supplements at any time-point up to 10 years on overall cognitive function (MD after a mean of 7.8 years -0.1 MMSE points, 95% CI -0.81 to 0.61) or the incidence of dementia (HR 0.94, 95% CI 0.72 to 1.24).	A long-duration study did not find any effect, but low quality evidence and not combined with omega 3.
Vitamin D-lung cancer	Vitamin D + calcium may result in little to no difference in lung cancer incidence in postmenopausal women (RR 0.90, 95% CI 0.39 to 2.08; 3 RCTs, 37601 women; low-certainty evidence).	Does the low dose of vitamin D in cod liver oil lung cancer indidence?

Benefit/Risk Assessment

Based on existing literature and data from Koronastudien, we have identified cod liver oil as a supplement that may prevent Covid-19 and or reduce the severity of the disease and found that the benefit of testing this in a randomized study far outweighs the risks.
A full benefit/risk assessment is found in the Ethics section.

3. Objectives and endpoints

Based on the encouraging results from Koronastudien as well as existing evidence from the literature, we aim to investigate whether cod liver oil can prevent Covid-19, serious Covid-19, or other respiratory tract infections.
We also aim to explore and confirm already known health effects and possible new health effects, in particular rare adverse events associated with cod liver oil use. This will be done during a follow-up period of up to two years after the end of the cod liver oil period

We hypothesize that:

Intake of cod liver oil can prevent Covid-19 disease
Intake of cod liver oil can prevent serious Covid-19
Intake of cod liver oil can prevent other airway infections

These hypotheses will be tested in a triple-blinded randomized placebo-controlled study where 80.000 participants will be assigned to cod liver oil or placebo in a 1:1 ratio.

The safety of cod liver oil will be explored.

Finally, it is a separate aim of the study to identify the mechanisms of action of any health effects seen.

Definition of endpoints

A. Number of participants diagnosed with serious Covid-19 (primary endpoint)

The number of participants with first time SARS-CoV-2 positive nasopharyngeal and or pharyngeal swabs (or any other sample used for detection of current disease) analyzed by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) nucleic acid amplification test or antigen tests [18] used by accredited Norwegian microbiology laboratories in the period from one week after the start of cod liver oil/placebo taking to the end of this period together with any of the following:

A) Self-reported dyspnea and fever concurrent (within four weeks) with the positive test
OR
B) hospitalization caused by Covid-19 concurrent (within four weeks) with the positive test
OR
C) death where the Covid-19 infection was wholly or partly responsible as judged by the death certificate (see endpoint in the protocol)

B. Number of participants diagnosed with New Covid-19 (primary endpoint):

The number of participants diagnosed with first time SARS-CoV-2 positive nasopharyngeal and or pharyngeal swabs (or any other sample used for detection of current disease) analyzed by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) nucleic acid amplification test or antigen tests used by accredited Norwegian microbiology laboratories from one week after the start of cod liver oil/placebo taking.

C. Number of participants with laboratory confirmed respiratory tract infection (primary endpoint):

An airway sample positive for a respiratory pathogen* (either PCR or culture) in the period from one week after the start of cod liver oil/placebo taking to the end of this period

*Influenza virus (A and B), parainfluenzavirus (1,2,3), metapneumovirus, rhinovirus, coronavirus (non-SARS), Respiratory Syncytial virus, Haemophilus Influenzae, Moraxella Catharralis, Streptococcus Pneumonia, Beta-hemolytic streptococci, Mycoplasma pneumonia, Chlamydophila pneumonia, Enterovirus, Bordetella pertussis. The list can be expanded based on the analyses performed in Norwegian Microbiology laboratories.

D. Number of participants with self-reported airway infection (primary endpoint)

The number of episodes with any two of the following symptoms in the period from one week after the start of cod liver oil/placebo taking to the end of this period:

- Fever
- Cough
- Nasal congestion
- Sore throat

Secondary endpoints

The testing of secondary endpoints will be described in the Statistical Analysis Plan.

A) Hospitalization for Covid-19

B) ICU care for Covid-19
C) Any admissions to hospital
D) Infection with each of the mentioned pathogens
E) Visits at GP for infections
F) Visits at GP

Exploratory during follow up of up to two years

- Cardiovascular disease incidence and mortality during the study period or follow up
- Cancer incidence and mortality during the study period or follow up
- All-cause mortality during the study period or follow up
- Fracture of the hip or forearm during the study period or follow up
- Incident dementia during the study period of follow up

Endpoints at six months:
All primary endpoints tested in the final statistical analysis plan will be tested six months after unblinding (the end of the cod liver oil or placebo taking period).

Safety

The safety of the intervention will be followed for two years after the end of the cod liver oil taking period. This will be done by observing all-cause mortality and hospital admissions for major disease groups in the cod liver oil versus the placebo group in Norwegian registries.

4. Study Design

Overall Design

The CLOC study will include 80.000 participants that will be randomized in a 1:1 ratio to consume 5 ml cod liver oil or placebo (corn oil) with lemon taste per day for 6-12 months.

The study will be organized as a ancillary study of "Koronastudien", a cohort study investigating Covid-19. Participants will be a subgroup of participants in Koronastudien, and relevant data from these participants will be shared among the studies.
Koronastudien has collected extensive electronic questionnaire data using the University of Oslo web-based solution "Nettskjema". Koronastudien aims to identify risk factors associated with the community- and workplace acquisition of Covid-19 virus and also aims to identify risk factors for the progression of the disease and to understand the virus and disease themselves.

Scientific Rationale for Study Design

Under the current pandemic with thousands of deaths daily worldwide, there is an urgent need to rapidly identify possibly safe and efficient preventive measures against Covid-19 and the complications of the disease. The study is designed to obtain such evidence in a timely manner without exposing the participants to unnecessary risk.

Justification for Dose

The most commonly used daily dose of cod liver oil is 5 ml and this dose will also be used in the study. This dose has been shown to increase the vitamin D levels of volunteers significantly, and contains the daily requirement of vitamin D in for most adults in Norway.

End of Study Definition

The End of study is defined as the last day of cod liver oil taking in the spring of 2021.
(Participants will still be followed after this date.)

5. Study population

Inclusion criteria

Any person >18 years with a Norwegian Personal Identity Number

Exclusion criteria

An electronic questionnaire will be used to collect self-reported data about exclusion criteria.

- History of renal failure or dialysis, hypercalcaemia, severe liver disease (chirrosis), sarcoidosis or other granulomataous disease (Wegener)
- Allergy to fish or corn oil.
- Pregnancy or planned pregnancy before summer 2021
- Vegan diet
- Age >75 years old at inclusion based on the Norwegian Personal Identity Number
- Difficulty of swallowing cod liver oil or other oils
- Previous Covid-19 disease
- For Caucasians only: Use of any supplement containing more than trace amounts of vitamin D or omega-3 fatty acids at inclusion (Vitamin D levels in non-Caucasians living in Norway are frequently low even among those self-reporting using dietary supplements).
    - This criteria will be relaxed if too few participants volunteers to the study and only Caucasians that use cod liver oil or an equivalent dietary supplement (with omega 3 and vitamin D) more than 5-7 times per week will be excluded.

Lifestyle Considerations

No restrictions are required

Recruitment

A large number of participants must be recruited in a short period of time. The following recruitment strategies will be employed:

1. The CLOC invitation letter and screening questionnaire will be sent to Koronastudien participants.
2. The CLOC study will be announced in media including on social media using text, pictures and video, and participants can volunteer to both studies on the study webpage. Participants recruited this way and not already in Koronastudien must also sign the Koronastudien consent form.

The electronic screening questionnaire will contain items to identify participants with exclusion criteria and will be completed during the same time as the consent form. A semi-automated review of all

screening questionnaires will be held, and any uncertainties will be clarified by contacting the respondents before final eligibility is decided and a study number assigned.

Screen Failures

Participants submitting the screening questionnaire and do not meet the study criteria will be reported as screen failures. They will not be assigned a study number and will not be rescreened.

6. Study Intervention

The study intervention is cod liver oil 5 ml daily or placebo (corn oil). Both will have lemon taste.

The cod liver oil will be the same as sold under the "Møllers Tran med Sitronsmak" brand.

Label

FOR CLINICAL TRIALS
Mollers Cod liver oil with lemon flavor / corn oil with lemon flavor
Dosage 5 ml once a day.
Taken with food in the morning. Store in a refrigerator.
Responsible for the study is Oslo University Hospital, Department of Microbiology, Section for Research, Forskningsveien 1, SINTEF Building, 0373 Oslo
transtudien@ous-hf.no
www.transtudien.no
Keep out of reach of children. Do not take more than the recommended dose. Dietary supplements do not replace a varied diet.
Best before the end of September 2022.
Numbering: xxx

Preparation/Handling/Storage/Accountability

The treatment oils are produced in colored flasks and will be delivered to participants by ordinary mail at room temperature. After reception, the cod liver oil/placebo should be kept in a refrigerator for the whole study period for optimal quality and taste. The product should be taken in the morning each day to increase compliance and preferably up to two forgotten doses can be taken together.

The participants will be presented with a way of measuring 5 ml of cod liver oil. At the end of the study each participant will be asked to measure the remaining product and report this.

Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding

Willing and eligible participants will be randomly assigned to one of two treatment groups: 5 ml of cod liver oil x1 per day or placebo together with the first meal each day.
Concealment of allocation: Randomization will be conducted on the Department of Research Support, Oslo University Hospital, by personnel not involved in the study. The list of participants with address and treatment assignment will be provided to the packaging company, which will send cod liver oil or placebo for the whole study period to each participant based on that list. The responsible personnel at the packaging company will not be involved in the study, and no personnel involved in the study will have access to this list.
The number of participants to be randomized: In the case of successful recruitment of an excess number of participants, participants belonging to high-risk groups (> 70 years old and dark-skinned) will be prioritized for randomization. The remaining non-randomized participants will be included as

an extra control group that will not receive any treatment but will otherwise be followed as the other participants and analyzed for the exploratory endpoints.
In the case fewer recruited participants than planned, Caucasians using cod liver oil or an equivalent supplement (vitamin D and omega 3) less frequently than 5 days per week can be included in the study We consider the risk of overdosing of omega 3 or vitamin D to be very low in this group and while the group will contribute less to the total power of the study than participants not using such supplements their intake will increase during the study period and they will contribute to the study. Based on data from Koronastudien we expect less than 20-30% such participants.

Unblinding

In the highly unlikely case of emergency unblinding this will be done the physician requiring unblinding contacting the PI and will be referred to the Research Support randomization team for information about treatment allocation.

Study Intervention Compliance

Our primary measure of compliance will be self-reported information provided on a monthly follow-up questionnaire, which will ask about adherence to the cod liver oil/placebo taking regimen. It has been reported that although most participants try diligently to adhere to the regimen, those who do not comply have no embarrassment about describing what they are actually doing. Blood levels have shown near-perfect correlations with self-reported questionnaire data on adherence[17]. Participants reporting taking more than 80% of the cod liver oil or placebo will be considered compliant.
Because CLOC participants will reside throughout Norway, it will not be possible to obtain blood samples for a validity study on all participants. Thus, at baseline, 2-months and after that every month we will invite randomly selected participants to provide a blood sample for biobanking and validation purposes. including measurement of 25(OH)D and EPA+DHA levels. The distribution of these values will be compared between the active and placebo groups, and compared with the questionnaire data on compliance, as a test for validity.
Additionally, we will be able to assess 25 (OH)D and EPA + DHA levels in the up to 10.000 randomly selected participants who will be asked to provide a blood sample at baseline and at the end of the study. These blood samples may be collected as dried blood spots and will also be used for other analyses.

Dose modification

No dose modification will be conducted, but participants can divide doses freely.

Continued Access to Study Medication after End of the Study

Tran is available in all Norwegian grocery stores and participants will be encouraged to follow Norwegian dietary advice.

Treatment of Overdose

N/A

Concomitant Therapy

Any drugs will be allowed together with the oils. However, use of supplements containing vitamin D and other contents of cod liver oil are expected to reduce the power of the study to show a difference between the treatment groups and will be recorded. Participants will be encouraged not to begin with new dietary supplements while in the study, but they can continue in the study if the choose to do

this. Participants will be referred to official Norwegian dietary advice online if they have questions about supplements or diet during the study period.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for relevant endpoints unless the participants want to also withdraw.

Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

The participant may also withdraw the consent to use some of his or her data as described in the consent form.

Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study and data on registries are no longer recorded (this will mostly be participants moving abroad).

8. Study Assessments and Procedures

Endpoint Ascertainment and Validation

Se also definition of endpoints in chapter 3.

Endpoint ascertainment will be done by obtaining endpoint data from relevant registries. The connection between the CLOC study and the registries will be made by the Norwegian Personal Identity Number (PIN), which ensures unambiguous identification of every subject. The PIN number is validated by 2-factor authentication when the informed consent is signed electronically.

Registry data will be compared to the self-reported symptoms. In cases where an episode of respiratory illness evidenced by a positive PCR or culture is not accompanied by a symptom report form, the patient will be encouraged to complete a symptom form.

Diagnoses in hospitalized patients and outpatient visits are reported to the Norwegian Patient Registry (NPR), while deaths are reported to the Causes of Death Registry.
Covid-19- related diagnoses and deaths in these registries are essential endpoints in the study and will be validated through inspection of the relevant hospital records (NPR) or hospital- or GP records (CDR). This will be done by contacting the hospital or GP for a copy of the relevant information from their records, which will be recorded in the CRF together with a conclusion about Covid-19 being the cause

of the hospitalization or death. The information will also be presented for another independent and blinded physician for a second opinion, and in cases of discrepancy; the information will further be inspected by a blinded endpoint-verification committee for a final decision. It will be arranged for the endpoint-verification committee to have access to interview the treating physician.

The endpoint of subjective dyspnea during Covid-19 will be based on self-reporting (yes/no).

Safety Assessment

Cod liver oil is recommended as a part of the Norwegian diet in official dietary recommendations and no safety assessment will be conducted during the cod liver oil/placebo taking period. See Ethics section.

Blood collection

Blood will be collected for the purpose of monitoring compliance and for the study itself. Blood will be collected according to the standard procedure described in Oslo University Hospitals' quality control system, and either venipuncture or dried blood spots will be used.

- Random blood collection for Compliance (either venipuncture or dried blood spot)
- Baseline and follow up for biobanking (either venipuncture or dried blood spot)
- Surplus material already stored in existing biobanks including treatment-biobanks will also be collected from the participants, and either stored in the study biobank or analyzed immediately (or both)

Blood samples will be analyzed for vitamin D levels (25(OH)D), EPA and DHA levels, and other biochemical parameters. The material will be stored in the study biobank for analyses to explore and explain the main results of the study. These analyses can include both biochemical, immunological, and molecular biology analyses and will be determined based on the results of the investigation.

Biobank

A study-specific biobank for the duration of the study until five years after all participants are dead will be created.
All blood- and other biological samples collected as part of the study will be stored in this biobank.

Questionnaires and consent forms

Participants will already have completed the Koronastudien questionnaires containing questions about risk factors for Covid-19, supplement use, travel history, cancer, cardiovascular disease, and other previous diseases, skin-type, sunlight exposure, and demographic variables). During the study period, it is expected that 1-2 Koronastudien specific follow-up questionnaires will be distributed, and these will be coordinated to reduce the burden of participation. In addition, the following data will be collected from the sub-study participants using electronic forms:

- Screening questionnaire before inclusion (inclusion and exclusion criteria)
- Consent form. The identity of each participant in Koronastudien is known through the consenting procedure using two-factor authentication with Bank ID. The consent form for Transtudien will be sent as a unique link to existing participants, and consenting will be a simple yes or no checkbox at the end of the form without requiring further identification with Bank ID.

- Baseline questionnaire: Diet including an estimate of vitamin D and n-3 LCPUFA intake, (using a validated web-based food frequency questionnaire (FFQ). Other baseline data collection will be coordinated with a follow-up questionnaire in Koronastudien to reduce participant burden.
- Every month: Compliance, use of supplements, side effects, efficacy of blinding, endpoints
- End of study: FFQ, risk factors for Covid-19 and other relevant diseases, use of supplements, previous conditions, side effects, efficacy of blinding, endpoints
- Follow-up up to two years: Diet, use of supplements, endpoints.

Participants will also be encouraged to report any symptoms of respiratory tract infections and any possible side-effect during the cod liver oil taking period using an electronic questionnaire available to them at all times during the study period.

Dietary questions on vitamin D and n-3 LCPUFA only can be made available for participants not willing to complete the full FFQ. This will be based on the FFQ.

Registries

Data for validation of endpoints, previous diseases, and risk factors will be obtained from the following registries (registry, data to be obtained):

- Causes of death: death, and cause of death
- Hospital records: verification of endpoints
- KUHR: visits to GP and cause of visit
- Norwegian Prescription database:, medications
- MSIS: Covid-19 status
- The Norwegian Patient Registry (NPR): Hospital admissions and outpatient visits: fractures, health-related events and endpoints
- The patients' general practitioner or treating physician may be contacted for verification of endpoints, adverse effects, and causes of death
- Luftveisdatabasen (Airway Database), Covid-19 status, other PCR and culture verified infections
- Microbiology laboratories, microbial test results not available through Airway Database (HelseNorge.no)
- Other statutory health registries including the Norwegian Pandemic Registry and heart registry
- Folkeregisteret and The Contact and Reservation Registry, contact information, address
- Quality Registries on Covid in Oslo University Hospital, detailed data about risk factors for Covid-19 and outcome of disease

Assessment of dietary and Supplemental Intake Questionnaire

A validated, self-administered semi-quantitative food frequency questionnaire (FFQ) will be distributed to participants at baseline. Classifying participants by baseline intake of various nutrients will allow us to evaluate whether the study agents' effects vary by such intake. Participants will also be asked to complete the questionnaire at the end of the study, enabling an examination of dietary changes over time.
Questions on the use of non-study supplements or drugs containing vitamin D or EPA+DHA will be asked at baseline and end of the study and on follow-up questionnaires. We will ascertain and analyze intake from food and supplements separately, and from both sources combined.

Follow up

At the end of the intervention, three, six months, 12 and 24 months later, a questionnaire will be sent to participants. The form will be similar to the conventional follow-up questionnaires, collecting

information about potential risk factors, major diseases use of medications, and medical history. The additional data will be used to address the duration of any effects seen on the primary endpoints and any side effects of the intervention as well as to explore other health effects of cod liver oil as described in the endpoint section.

Data management

The handling data will be closely connected to the handling of data in Koronastudien, and for data handling purposes, the CLOC study will be treated as a sub-study of Koronastudien. An application to process and store data from the two studies together will be sent to the Data Protection Officer at Oslo University Hospital. Koronastudien has been approved by the Data Protection Officer at Oslo University Hospital in accordance with the European GDPR regulations.

The University of Oslo service for sensitive data (TSD) will be used to collect, store, and analyze data. Additionally, HUNT cloud and LEDIDI Prjcts will be used for analyzing data. The data will be analyzed without any directly personally identifying information using a Study ID instead. The patient list connecting the patient identity with the study ID will be kept in a separate folder in TSD, and the backup will be kept at an encrypted USB data storage device. Deidentified data will be backed up at K:/sensitive, a secure location at the Oslo University Hospital's internal web.

9. Statistical considerations

The detailed statistical analysis plan will be approved by the study steering committee before unblinding.

Statistical Hypotheses

See Sample Size Determination and the statistical analysis plan

Sample Size Determination

The fallback method (https://www.fda.gov/media/102657/download) will be used to correct for testing of multiple primary endpoints.

The total alpha (0.05) will be divided among the endpoints, and a fixed sequence for the testing will be maintained. As the testing sequence progresses, a successful test preserves its assigned alpha as “saved” (unused) alpha that is passed along to the next test in the sequence. This passed-along alpha is added to the assigned alpha of the next endpoint, and the summed alpha is used for testing that endpoint. Thus, as sequential tests are successful, the alpha accumulates for the endpoints later in the sequence; these endpoints are then tested with progressively larger alphas.

Endpoints in testing order with power calculation:

1. Serious Covid-19 (Covid-19 with dyspnea, hospitalization, or death). Assigned α=0.018.
   Based on the observations in Koronastudien of a 40% reduction in serious Covid-19 in the group reporting use of cod liver oil, and an expected incidence of 0.25%, a power of 70%, 67,000 participants will have to be included for this endpoint.
2. Covid-19 positive PCR. Assigned α=0.03.
   Based on the observations in Koronastudien of a 20% reduction in Covid-19 incidence in the group reporting use of cod liver oil, and an expected incidence of 1%, a power of 70%, 65,000 participants will have to be included for this endpoint.
3. Positive PCR or bacterial culture for an airway pathogen. Assigned α=0.001.

Based on the expected frequency of airway infections in Koronastudien of >30% and a high (25%) expected testing frequency in Norway due to Covid-19 testing as well as a threshold of clinically interesting reduction of airway infections of 20%, 20,000 participants will have to be included for this endpoint. The study has a power for this endpoint >95%. 15000 participants in the study will give an 80% power for this endpoint.

4. Self-reported airway infection. Assigned α=0.001.
   Based on the expected frequency of airway infections in Koronastudien of >30% and as a threshold of clinically interesting reduction of all airway infections of 10%, 23,000 participants will have to be included for this endpoint. The study has a power for this endpoint >95%. 16000 participants in the study will give an 80% power for this endpoint.

Analysis sets

Participants will be assigned to the cod liver oil or placebo group in a 1:1 ratio. The primary endpoints will be calculated using relative risks, Kaplan-Meier plots and Cox regression on the intention to treat (ITT) population with missing data on outcome counting as the negative outcome.

Compliance with cod liver oil taking and power of the study

The power calculation is based on data from Koronastudien and participants reporting taking cod liver oil. We have no data on how often cod liver oil was used by these participants but believe that it is less than once daily on average. Thus, although many participants in the CLOC study will not be fully compliant, we expect that a large majority of participants will have the same level of cod liver oil taking as found in Koronastudien. However, to increase the power, we will attempt to recruit up to 80.000 participants to increase the power of the study.

Interim Analyses

Covid-19-prevalence and power

The power of the study is dramatically influenced by the incidence of Covid-19, and this will be considered when the statistical analysis plan is finalized before unblinding to maximize the scientific output of the study. Thus, the statistical analyses including p-values and testing-order above can be changed if the Covid-19 situation dictates such changes. Any change will be done before unblinding. The time of unblinding can be changed based on the prevalence of Covid-19 to increase the scientific output from the study. No interim analyses will be conducted.

10. Ethics

Risks in the cod liver oil group

Cod liver oil has been used as a supplement for more than 100 years and thus has an excellent safety record. It is explicitly mentioned under the seafood category in official Norwegian dietary advice (https://helsenorge.no/kosthold-og-ernaring/kostrad/spis-fisk-oftere) The main constituents, vitamin D and omega 3 have been used in tens of thousands of participants in well-designed studies with very few side effects [4, 8]. The risk of overdosing is very low because of the relatively large volume of oil that has to be ingested for overdosing.

In a Norwegian study with a similar design as the proposed study also with cod liver oil, it was found that 5 ml of cod liver oil increased the vitamin D level with 17 nmol/liter. This is a moderate increase that will have a very low probability of toxicity, yet still be large enough to treat vitamin D deficiency[9]. To further ensure participants' safety, we will exclude from the trial persons with a history of kidney stones, hypercalcemia, renal failure, cirrhosis, or sarcoidosis or other granulomatous diseases and persons belonging to groups advised to use a vitamin D supplement.

We expect no adverse events related to taking cod liver oil and although possible adverse health effects will be monitored as part of the study, adverse events during the cod liver oil taking period will be expected to be followed up as part of normal care by the relevant health professionals and will not be followed up or reported as part of the study.

Risks in the placebo group

Volunteers older then 75 years old are advised use a vitamin D supplement , according to official dietary advice, and will be excluded from the study in the screening phase and receive an automated message about the official advice if they do not report taking and supplement.

The study aims to identify the health effects of cod liver oil as a supplement to the normal diet of participants not normally using such supplements. Most people have a relatively stable diet over many years, and the study will attempt not to interfere with the diet of participants. We consider that continuing to have the same diet as before during a study period that lasts less than one year poses a negligible risk to participants.
However, the Norwegian dietary recommendations for vitamin D are complicated and depend on how much fish you eat, your age, the season, and your sun exposure. Based on the collected data, participants at high risk for vitamin D or low levels of n2-LCPUFFA will be notified at the end of the study and recommended to discuss their diet with their general practitioner and or get their vitamin D levels and 3n-LCPUFA levels measured.

No measurements of vitamin D or 3n-LCPUFA will be made before unblinding, and this will not be known to the study during the cod liver oil/placebo taking period.

Expected side-effects

Several side-effects have been described for intake of fish oil and low-dose vitamin D, but in practice, very few serious side effects are expected to be found.
For fish oil the following side effects have been described: gastrointestinal (GI) symptoms (stomach upset or pain, nausea, constipation, diarrhea), bleeding (any GI bleed, GI bleeding requiring transfusion, hematuria, easy bruising, epistaxis), skin rash, colds or upper respiratory tract infection, flu-like symptoms, bad taste in the mouth
For vitamin D, the following side effects have been described: GI symptoms as listed above, and hypercalcemia or kidney stones.
Each follow-up questionnaire will contain questions about side-effects.

Importance of study results and generalizability

There is a significant inherent risk in the study that the Covid-19 prevalence becomes much lower than the threshold for detection of any effect or that a Covid-19 cure or vaccine becomes available, making the study results less relevant. However, the primary endpoints of respiratory tract infections will still be of great importance; likewise, the in-depth safety characterization of cod liver oil will be of importance.

Benefits

The main benefit of the study is to identify a new and safe way to prevent Covid-19 or its complications. Furthermore, the study is powered to detect whether cod liver oil can prevent respiratory infections.
In addition, the study is well suited to compare positive or negative health effects of cod liver oil In particular, the systematic collection of negative health effects that will be conducted is important to ensure the two year safety of this widely used supplement.

Surveying of risks

A survey of risks of the study will be conducted by the PI and in collaboration with the Department of Research Support, OUH and identified risks will be addressed before the beginning of the cod liver oil taking period.

Ethics summary

In conclusion, the study has a low risk of negative health- or other effects on participants and a high probability of identifying whether cod liver oil can prevent Covid-19 and other respiratory infections. Furthermore, the encouraging preliminary data suggests that the morbidity caused by Covid-19 will be significantly reduced in the cod liver oil group adding to the benefit of the study. Further adding to the benefit is the prospect of collecting high-quality data on the more general health effects of cod liver oil use.

In total, we consider that the benefits of the study far outweigh the risks and disadvantages.

10. 1 Study Administration and Financial Statement

Responsible for the study

Oslo University Hospital is responsible for the study. Arne Søraas, MD, PhD is the PI of the study. The study is a collaboration between OUH, UIO and NIPH.

Steering committee

The PI will appoint a steering committee with representatives from OUH, University of Oslo and the Norwegian Institute of Public Health (NIPH) that will meet regularly during the study period and give advice to the PI in conducting the study. A patient representative will participate in this committee. At the time of writing the steering committee members are: Arne Søraas, OUH (PI), Professor Stine Ulven, UiO, professor Haakon E. Meyer (UiO, NIPH), professor Anette Hjartåker (UiO), professor Kirsten Bjørklund Holven, (UiO). The user representative is Turid Wøien. Secretary: Mette Istre (OUH).

Monitoring of data quality

The Department of Research Support at Oslo University Hospital will monitor the data quality of the study and randomization.
A statistician from the OUH/UIO statistical research support department will write the statistical analysis plan together with the PI and perform the primary analyses.

All study personal will be obliged to attend to a good clinical practice course. The PI has the Human Subject Research CITI certification.

Financing

The study will be financially supported by Orkla Health, which owns the “Møllers Tran”, a widely used cod liver oil brand. The financing will cover most of the expenses for Oslo University Hospital in 2020 and 2021 as well as producing and distributing cod liver oil to the participants and marketing of the study.
The study was initiated by Oslo University Hospital and Koronastudien, who contacted Orkla Health for financing the project.
Orkla Health will not have any influence on the choice of data analyses or publication of study results.

The study aims to attract funding from both private and government sources.

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Protocol for the Cod Liver Oil for Covid-19 Prevention Study

Contents

Title

A randomized, parallel-group treatment, participant, investigator, care provider and outcomes assessor masked, two-arm study to assess the effectiveness of cod liver oil compared to placebo in the prevention of Covid-19 and airway infections in healthy adults

Short: Cod Liver Oil for Covid-19 Prevention Study

Shorter: Transtudien

Sponsor and contact details

Sponsor:

Oslo University Hospital, PB 4959 Nydalen, 0424, Oslo

Principal Investigator (PI):

Arne Søraas, MD, PhD
Oslo University Hospital, Department of Microbiology, Section of Research
PB 4959 Nydalen, 0424, Oslo
Email: arne.vasli.lund.soraas@rr-research.no
Phone: +47 90652904

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
1.0: First complete REK approved protocol.	*Completed October 5. Approved October 12, 2020*
1.01:	Completed October 22, 2020
1.02	Completed October 27. 2020
1.1	Completed November 30, 2020

1.2	Completed November 10. 2021

Amendment 1 (October 22, 2020)

Use of antigen tests added as these have a very high specificity [18].
Change of full study title: addition of randomized, placebo and airway infections.
Follow up period for definition of serious Covid-19 disease changed from 8 to 4 weeks.

Amendment 2 (October 27, 2020)

Norwegian label translated.
Endpoints described according to ClinicalTrials standard
Endpoints at 12 months moved from secondary endpoints to exploratory endpoints.

Amendment 3 (November 30, 2020)

We have interpreted the Exclusion criteria about cod liver oil in Caucasians as Caucasians that use vitamin D cannot or cod liver oil 5-7 times per week can not be included, while use of omega 3 only is acceptable for inclusion. This is not directly clear from the text as it is written.

Amendment 4 (November 10, 2021)

Follow up period for definition of serious Covid-19 disease changed from 4 weeks to 'in the period around the positive SARS-CoV-2 test. Removed fever as an endpoint for serious Covid-19 disease.
Primary endpoint 'laboratory verified respiratory infections' replaced with 'negative SARS-CoV-2 tests'. *'Laboratory verified respiratory infections' moved to secondary endpoints.*
Study compliance, blood sampling changed from monthly to after 3-4 months after start cod liver oil/placebo.
Simple dietary questions on vitamin D and LCPUFA n-3 food sources at baseline instead of a full FFQ.
Definition of compliant participants changed.
Other minor changes.

1. Protocol Summary

Preliminary evidence from literature and an ongoing study in our lab suggests that cod liver oil may prevent Covid-19 and complications of Covid-19. We will investigate whether this is actually the case or in "Transtudien" by randomizing volunteers to take cod liver oil or placebo (corn oil) during the winter months of 2020-2021.

Schema

June-September 2020: Study design and approvals phase
September-October 2020: Screening and inclusion of participants
October 2020-April 2021: Cod liver oil or placebo taking period
November 2020-April 2021: Obtain registry data
May 2021: Compiling data and publish results
November 2021: End of follow up
2030: End of study.

2035 Destruction of patient list.

2. Introduction

Study Rationale and background

Cod liver oil is an important source of long-chain omega-3 polyunsaturated fatty acids (n-3 LCPUFA), in particular, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), and vitamin D. It is an important supplement for people who do not eat fatty fish as recommended by the Norwegian authorities. The health benefits of EPA and DHA are well documented, indicating protective effects on cardiovascular disease (CVD) and the immune system [1-4]

Vitamin D acts on nuclear receptors on multiple locations and have a wide range of short- and long term effects, including the prevention of rickets, asthma exacerbations [5], and importantly acute respiratory tract infections [6, 7].

The health effects of a combination of polyunsaturated fatty acids with and without vitamin D have recently been investigated in the VITAL study, which included 25,000 participants over five years. No serious safety concerns were noted, although all-cause mortality remained unchanged [4, 8].

In a recent report from Ernæringsrådet (2018), a Norwegian government agency, it was found that low levels of vitamin D were prevalent in the Norwegian population, and it was recommended that all dairy products and plant-based substitutes should be fortified with vitamin D. Cod liver oil is mentioned in Norwegian official dietary advice as an important source of n-3 LCPUFA.

In the Cod Liver Oil for Covid-19 Prevention study (CLOC), 80.000 participants will be randomized to cod liver oil or placebo, aiming to prevent Covid-19 and its complications.

The study is initiated by Oslo University Hospital and is a collaboration with the University of Oslo, the National Institute of Public Health and is partially financed by Orkla Health.

Cod Liver Oil

Fish oils or fat fish are important sources of vitamin D and n-3 LCPUFA in the diet. Cod liver oil contains 10 ug of vitamin D and 1 g of polyunsaturated fatty acids (DHEA 0,6g and EPA 0,4g) per 5 ml and covers the daily requirements for these nutrients with a low risk of overdosing and with a safety profile established through more than 100 years of use. The supplement is widely used in Norway and abroad, and more than 5 million bottles of “Møllers tran”, a widely used brand, are produced each year.

The health effects of cod liver oil have been investigated before, including in a randomized controlled study in Norway [9]. However, to our knowledge, no extensive safety studies have been conducted on cod liver oil. Also, most studies are done on either vitamin D or n-3 LCPUFA, and the health effects of the widely used supplement cod liver oil compared to each of these constituents have, to our knowledge, not been described in randomized studies.

Covid-19

Covid-19, the disease caused by the pandemic SARS-CoV-2 virus in 2020, has infected more than 14 million people worldwide and killed more than 0.6 million (Worlometers.info, July 18, 2020).

The most common cause of death is respiratory failure, and most hospitalized patients need extra oxygen supply, and some need mechanical respiratory support in intensive care units. A prominent hypothesis for the pathophysiology of the SARS-CoV-2 virus is that overreaction from the immune system against the virus – a cytokine storm – is involved in causing the lung damage and the life-threatening complications of the disease [10, 11].

Cod liver oil in Covid-19

Vitamin D supplement has been shown to prevent asthma exacerbations and respiratory tract infections [5, 6]. In particular, people with low levels of vitamin D before supplementation benefited. Furthermore, Vitamin D deficiency has been associated with severe disease outcomes and death in

Covid-19, and several studies are investigating the use of vitamin D to prevent these outcomes in Covid-19 [12-14](ClinicalTrials.org).
However, not all studies on vitamin D and Covid-19 are positive, and a large UK biobank study found no association between vitamin D levels ten years ago and Covid-19[15].
Omega 3 long-chain fatty acids have immunomodulatory effects and have been shown to be possibly beneficial when given to patients with respiratory support in intensive care units[16].
The safety of the low doses of vitamin D and n-3 LCPUFA in cod liver oil has been proven in multiple studies [4, 8, 9].

Thus, current literature support that the low levels of vitamin D found in cod liver oil may be sufficient to mediate a protective effect against respiratory tract infections. However, this has not been shown in randomized studies on Covid-19, and the evidence is not unambiguous.
Literature also supports that n-3 LCPUFA may have some additional benefits in respiratory infections and that cod liver oil has an excellent safety profile.

Koronastudien

In Koronastudien, 140.000 participants have answered a questionnaire about their use of dietary supplements, demographics, airway symptoms, and risk factors for Covid-19.
In univariate analyses, we have found that participants using vitamin D and or cod liver oil were associated with a reduced risk of Covid-19 (OR 0.8, p<0.001) and of serious (hospitalized) Covid-19 with hospitalization (OR 0.3, p=0.07).
These protective effects are also seen in preliminary analyses of cod liver oil alone when age, gender, and contact with Covid-19 patients are included in the analyses (OR 0.6, p=0.02) for Covid-19 disease with dyspnea and OR 0.1, p=0.03 for hospitalized Covid-19 disease.

Other short-term health effects of cod liver oil

Cod liver oil and the major constituents, vitamin D and n-3 LCPUFA, have been investigated for a long list of conditions over many years. They have been found to be safe, but many studies have been underpowered to detect smaller effects on health and many need to be validated in new datasets. Our study will not be powered to make conclusions on health effects of cod liver oil, but as exploratory endpoints validating existing findings the randomized data obtained will be of great value both at the end of the cod liver oil taking period and for up to two years which is the follow up period of the study.

In total, 70 Cochrane reviews includes vitamin D and 48 includes omega 3. The most relevant research questions for the CLOC study are:

Intervention	**Cochrane conclusion**	**CLOC study relevancy**
Omega 3-dementia	Considering this and the fact that omega-3 PUFA cannot be synthesised by humans, omega-3 PUFAs might be a promising treatment option for dementia.	Incidence of new dementia in cod liver oil group.
PUFA (including Omega 3)-primary and secondary prevention of cardiovascular disease	Increasing PUFA intake …probably slightly reduces risk of coronary heart disease events from 14.2% to 12.3% (RR 0.87, 95% CI 0.72 to 1.06, 15 trials, 10,076 participants) Increasing PUFA intake probably slightly reduces risk of coronary heart disease and cardiovascular disease events, may slightly reduce risk of coronary heart	Incidence of cardiovascular diseases in cod liver oil group.

	disease mortality and stroke (though not ruling out harms), but has little or no effect on all-cause or cardiovascular disease mortality.	
Vitamin D-cancer prevention	There is currently no firm evidence that vitamin D supplementation decreases or increases cancer occurrence… Vitamin D_3 supplementation decreased cancer mortality and vitamin D supplementation decreased all-cause mortality, but these estimates are at risk of type I errors due to the fact that too few participants were examined, and to risks of attrition bias originating from substantial dropout of participants.	Incidence of new cancer diagnoses in the cod liver oil group.
Vitamin D-all-cause mortality	Vitamin D3 seemed to decrease ….. Because of risks of attrition bias originating from substantial dropout of participants and of outcome reporting bias due to a number of trials not reporting on mortality, as well as a number of other weaknesses in our evidence, further placebo-controlled randomised trials seem warranted.	Does the low dose of vitamin D in cod liver oil reduce mortality?
Vitamin D-fractures	There is high quality evidence that vitamin D plus calcium is associated with a statistically significant reduction in incidence of new non-vertebral fractures. However, there is only moderate quality evidence of an absence of a statistically significant preventive effect on clinical vertebral fractures.	Other fractures was not prevented, but no large studies on cod liver oil exist (Meyer et al 1999)
Vitamin D-dementia	One trial with 4143 participants compared vitamin D3 (400 IU/day) and calcium supplements to placebo. We found low- to moderate-certainty evidence of no effect of vitamin D3 and calcium supplements at any time-point up to 10 years on overall cognitive function (MD after a mean of 7.8 years -0.1 MMSE points, 95% CI -0.81 to 0.61) or the incidence of dementia (HR 0.94, 95% CI 0.72 to 1.24).	A long-duration study did not find any effect, but low quality evidence and not combined with omega 3.
Vitamin D-lung cancer	Vitamin D + calcium may result in little to no difference in lung cancer incidence in postmenopausal women (RR 0.90, 95% CI 0.39 to 2.08; 3 RCTs, 37601 women; low-certainty evidence).	Does the low dose of vitamin D in cod liver oil lung cancer indidence?

Benefit/Risk Assessment

Based on existing literature and data from Koronastudien, we have identified cod liver oil as a supplement that may prevent Covid-19 and or reduce the severity of the disease and found that the benefit of testing this in a randomized study far outweighs the risks.
A full benefit/risk assessment is found in the Ethics section.

3. Objectives and endpoints

Based on the encouraging results from Koronastudien as well as existing evidence from the literature, we aim to investigate whether cod liver oil can prevent Covid-19, serious Covid-19, or other respiratory tract infections.
We also aim to explore and confirm already known health effects and possible new health effects, in particular rare adverse events associated with cod liver oil use. This will be done during a follow-up period of up to two years after the end of the cod liver oil period

We hypothesize that:

Intake of cod liver oil can prevent Covid-19 disease
Intake of cod liver oil can prevent serious Covid-19
Intake of cod liver oil can prevent other airway infections

These hypotheses will be tested in a triple-blinded randomized placebo-controlled study where 80.000 participants will be assigned to cod liver oil or placebo in a 1:1 ratio.

The safety of cod liver oil will be explored.

Finally, it is a separate aim of the study to identify the mechanisms of action of any health effects seen.

Definition of endpoints

A. Number of participants diagnosed with serious Covid-19 (primary endpoint)

The number of participants with first time SARS-CoV-2 positive nasopharyngeal and or pharyngeal swabs (or any other sample used for detection of current disease) analyzed by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) nucleic acid amplification test or antigen tests [18] used by accredited Norwegian microbiology laboratories in the period from one week after the start of cod liver oil/placebo taking to the end of the study period together with any of the following:

A) Self-reported dyspnea concurrent with the positive test
OR
B) self-reported hospitalization caused by Covid-19 concurrent with the positive test
OR
C) death where the Covid-19 infection was wholly or partly responsible as judged by the death certificate, information from relatives or hospital records (see endpoint in the protocol)

B. Number of participants diagnosed with New Covid-19 (primary endpoint):

The number of participants diagnosed with first time SARS-CoV-2 positive nasopharyngeal and or pharyngeal swabs (or any other sample used for detection of current disease) analyzed by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) nucleic acid amplification test or antigen tests used by accredited Norwegian microbiology laboratories from one week after the start of cod liver oil/placebo taking.

C. A negative SARS-CoV-2 test (primary endpoint)

Covid tests (SARS-CoV-2), real time (RT)-PCR, are mostly obtained because of a suspicion of COVID-19. The number of negative covid tests from one week after starting taking cod liver oil/placebo and to the end of the intervention period. This endpoint has been added as an alternative to the Positive PCR or bacterial culture endpoint (below, secondary endpoint, which is not available at this time).

D. Number of participants with self-reported airway infection (primary endpoint)

The number of self-reported airway infections in the period from one week after starting taking cod liver oil/placebo to the end of the intervention period.

Secondary endpoints

The testing of secondary endpoints will be described in the Statistical Analysis Plan.

A) Hospitalization for Covid-19
B) ICU care for Covid-19
C) Any admissions to hospital
D) Infection with each of the mentioned pathogens
E) Visits at GP for infections
F) Visits at GP
G) Laboratory confirmed respiratory tract infection (previous primary endpoint)

G) *Number of participants with laboratory confirmed respiratory tract infection (this is a previous primary endpoint, which will be studied later when data from laboratories are available):*

An airway sample positive for a respiratory pathogen* (either PCR or culture) in the period from one week after the start of cod liver oil/placebo taking to the end of this period

*Influenza virus (A and B), parainfluenzavirus (1,2,3), metapneumovirus, rhinovirus, coronavirus (non-SARS), Respiratory Syncytial virus, Haemophilus Influenzae, Moraxella Catharralis, Streptococcus Pneumonia, Beta-hemolytic streptococci, Mycoplasma pneumonia, Chlamydophila pneumonia, Enterovirus, Bordetella pertussis. The list can be expanded based on the analyses performed in Norwegian Microbiology laboratories.

Exploratory during follow up of up to two years

- Cardiovascular disease incidence and mortality during the study period or follow up
- Cancer incidence and mortality during the study period or follow up
- All-cause mortality during the study period or follow up
- Fracture of the hip or forearm during the study period or follow up
- Incident dementia during the study period of follow up

Endpoints at six months:
All primary endpoints tested in the final statistical analysis plan will be tested six months after unblinding (the end of the cod liver oil or placebo taking period).

Safety

The safety of the intervention will be followed for two years after the end of the cod liver oil taking period. This will be done by observing all-cause mortality and hospital admissions for major disease groups in the cod liver oil versus the placebo group in Norwegian registries.

4. Study Design

Overall Design

The CLOC study will include 80.000 participants that will be randomized in a 1:1 ratio to consume 5 ml cod liver oil or placebo (corn oil) with lemon taste per day for 6-12 months.

The study will be organized as a ancillary study of "Koronastudien", a cohort study investigating Covid-19. Participants will be a subgroup of participants in Koronastudien, and relevant data from these participants will be shared among the studies.
Koronastudien has collected extensive electronic questionnaire data using the University of Oslo web-based solution "Nettskjema". Koronastudien aims to identify risk factors associated with the community- and workplace acquisition of Covid-19 virus and also aims to identify risk factors for the progression of the disease and to understand the virus and disease themselves.

Scientific Rationale for Study Design

Under the current pandemic with thousands of deaths daily worldwide, there is an urgent need to rapidly identify possibly safe and efficient preventive measures against Covid-19 and the complications of the disease. The study is designed to obtain such evidence in a timely manner without exposing the participants to unnecessary risk.

Justification for Dose

The most commonly used daily dose of cod liver oil is 5 ml and this dose will also be used in the study. This dose has been shown to increase the vitamin D levels of volunteers significantly, and contains the daily requirement of vitamin D in for most adults in Norway.

End of Study Definition

The End of study is defined as the last day of cod liver oil taking in the spring of 2021.
(Participants will still be followed after this date.)

5. Study population

Inclusion criteria

Any person >18 years with a Norwegian Personal Identity Number

Exclusion criteria

An electronic questionnaire will be used to collect self-reported data about exclusion criteria.

- History of renal failure or dialysis, hypercalcaemia, severe liver disease (chirrosis), sarcoidosis or other granulomataous disease (Wegener)
- Allergy to fish or corn oil.
- Pregnancy or planned pregnancy before summer 2021
- Vegan diet
- Age >75 years old at inclusion based on the Norwegian Personal Identity Number
- Difficulty of swallowing cod liver oil or other oils
- Previous Covid-19 disease
- For Caucasians only: Use of any supplement containing more than trace amounts of vitamin D or omega-3 fatty acids at inclusion (Vitamin D levels in non-Caucasians living in Norway are frequently low even among those self-reporting using dietary supplements).

- This criteria will be relaxed if too few participants volunteers to the study and only Caucasians that use cod liver oil or an equivalent dietary supplement (with vitamin D) more than 5-7 times per week will be excluded. Furthermore, Caucasians that use supplements with omega-3 fatty acids will not be excluded.

Lifestyle Considerations

No restrictions are required

Recruitment

A large number of participants must be recruited in a short period of time. The following recruitment strategies will be employed:

1. The CLOC invitation letter and screening questionnaire will be sent to Koronastudien participants.
2. The CLOC study will be announced in media including on social media using text, pictures and video, and participants can volunteer to both studies on the study webpage. Participants recruited this way and not already in Koronastudien must also sign the Koronastudien consent form.

The electronic screening questionnaire will contain items to identify participants with exclusion criteria and will be completed during the same time as the consent form. A semi-automated review of all screening questionnaires will be held, and any uncertainties will be clarified by contacting the respondents before final eligibility is decided and a study number assigned.

Screen Failures

Participants submitting the screening questionnaire and do not meet the study criteria will be reported as screen failures. They will not be assigned a study number and will not be rescreened.

6. Study Intervention

The study intervention is cod liver oil 5 ml daily or placebo (corn oil). Both will have lemon taste.

The cod liver oil will be the same as sold under the “Møllers Tran med Sitronsmak” brand.

Label

FOR CLINICAL TRIALS
Mollers Cod liver oil with lemon flavor / corn oil with lemon flavor
Dosage 5 ml once a day.
Taken with food in the morning. Store in a refrigerator.
Responsible for the study is Oslo University Hospital, Department of Microbiology, Section for Research, Forskningsveien 1, SINTEF Building, 0373 Oslo
transtudien@ous-hf.no
www.transtudien.no
Keep out of reach of children. Do not take more than the recommended dose. Dietary supplements do not replace a varied diet.
Best before the end of September 2022.
Numbering: xxx

Preparation/Handling/Storage/Accountability

The treatment oils are produced in colored flasks and will be delivered to participants by ordinary mail at room temperature. After reception, the cod liver oil/placebo should be kept in a refrigerator

for the whole study period for optimal quality and taste. The product should be taken in the morning each day to increase compliance and preferably up to two forgotten doses can be taken together.

The participants will be presented with a way of measuring 5 ml of cod liver oil. At the end of the study each participant will be asked to measure the remaining product and report this.

Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding

Willing and eligible participants will be randomly assigned to one of two treatment groups: 5 ml of cod liver oil x1 per day or placebo together with the first meal each day.
Concealment of allocation: Randomization will be conducted on the Department of Research Support, Oslo University Hospital, by personnel not involved in the study. The list of participants with address and treatment assignment will be provided to the packaging company, which will send cod liver oil or placebo for the whole study period to each participant based on that list. The responsible personnel at the packaging company will not be involved in the study, and no personnel involved in the study will have access to this list.
The number of participants to be randomized: In the case of successful recruitment of an excess number of participants, participants belonging to high-risk groups (> 70 years old and dark-skinned) will be prioritized for randomization. The remaining non-randomized participants will be included as an extra control group that will not receive any treatment but will otherwise be followed as the other participants and analyzed for the exploratory endpoints.
In the case fewer recruited participants than planned, Caucasians using cod liver oil or an equivalent supplement (vitamin D and omega 3) less frequently than 5 days per week can be included in the study We consider the risk of overdosing of omega 3 or vitamin D to be very low in this group and while the group will contribute less to the total power of the study than participants not using such supplements their intake will increase during the study period and they will contribute to the study. Based on data from Koronastudien we expect less than 20-30% such participants.

Unblinding

In the highly unlikely case of emergency unblinding this will be done the physician requiring unblinding contacting the PI and will be referred to the Research Support randomization team for information about treatment allocation.

Study Intervention Compliance

Our primary measure of compliance will be self-reported information provided on a monthly follow-up questionnaire, which will ask about adherence to the cod liver oil/placebo taking regimen. It has been reported that although most participants try diligently to adhere to the regimen, those who do not comply have no embarrassment about describing what they are actually doing. Blood levels have shown near-perfect correlations with self-reported questionnaire data on adherence[17]. Participants reporting taking cod liver oil or placebo more than two months will be considered compliant.
Because CLOC participants will reside throughout Norway, it will not be possible to obtain blood samples for a validity study on all participants. Thus, at baseline and approximately 3-4-months after starting taking cod liver oil/placebo we will invite randomly selected participants to provide a blood sample for biobanking and validation purposes, including measurement of 25(OH)D and EPA+DHA levels. The distribution of these values will be compared between the active and placebo groups, and compared with the questionnaire data on compliance, as a test for validity.
Additionally, we will be able to assess 25 (OH)D and EPA + DHA levels in the up to 10.000 randomly selected participants who will be asked to provide a blood sample at baseline and at the end of the

study. These blood samples may be collected as dried blood spots and will also be used for other analyses.

Dose modification

No dose modification will be conducted, but participants can divide doses freely.

Continued Access to Study Medication after End of the Study

Tran is available in all Norwegian grocery stores and participants will be encouraged to follow Norwegian dietary advice.

Treatment of Overdose

N/A

Concomitant Therapy

Any drugs will be allowed together with the oils. However, use of supplements containing vitamin D and other contents of cod liver oil are expected to reduce the power of the study to show a difference between the treatment groups and will be recorded. Participants will be encouraged not to begin with new dietary supplements while in the study, but they can continue in the study if the choose to do this. Participants will be referred to official Norwegian dietary advice online if they have questions about supplements or diet during the study period.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for relevant endpoints unless the participants want to also withdraw.

Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

The participant may also withdraw the consent to use some of his or her data as described in the consent form.

Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study and data on registries are no longer recorded (this will mostly be participants moving abroad).

8. Study Assessments and Procedures

Endpoint Ascertainment and Validation

Se also definition of endpoints in chapter 3.

Endpoint ascertainment will be done by obtaining endpoint data from relevant registries. The connection between the CLOC study and the registries will be made by the Norwegian Personal Identity Number (PIN), which ensures unambiguous identification of every subject. The PIN number is validated by 2-factor authentication when the informed consent is signed electronically.

Registry data will be compared to the self-reported symptoms. In cases where an episode of respiratory illness evidenced by a positive PCR or culture is not accompanied by a symptom report form, the patient will be encouraged to complete a symptom form.

Diagnoses in hospitalized patients and outpatient visits are reported to the Norwegian Patient Registry (NPR), while deaths are reported to the Causes of Death Registry.
Covid-19- related diagnoses and deaths in these registries are essential endpoints in the study and will be validated through inspection of the relevant hospital records (NPR) or hospital- or GP records (CDR). This will be done by contacting the hospital or GP for a copy of the relevant information from their records, which will be recorded in the CRF together with a conclusion about Covid-19 being the cause of the hospitalization or death. The information will also be presented for another independent and blinded physician for a second opinion, and in cases of discrepancy; the information will further be inspected by a blinded endpoint-verification committee for a final decision. It will be arranged for the endpoint-verification committee to have access to interview the treating physician.

The endpoint of subjective dyspnea during Covid-19 will be based on self-reporting (yes/no), but Covid-19 diagnosis is verified by the Norwegian Surveillance System for Communicable Diseases (MSIS).

Safety Assessment

Cod liver oil is recommended as a part of the Norwegian diet in official dietary recommendations and no safety assessment will be conducted during the cod liver oil/placebo taking period. See Ethics section.

Blood collection

Blood will be collected for the purpose of monitoring compliance and for the study itself. Blood will be collected according to the standard procedure described in Oslo University Hospitals' quality control system, and either venipuncture or dried blood spots will be used.

- Random blood collection for Compliance (either venipuncture or dried blood spot)
- Baseline and follow up for biobanking (either venipuncture or dried blood spot)
- Surplus material already stored in existing biobanks including treatment-biobanks will also be collected from the participants, and either stored in the study biobank or analyzed immediately (or both)

Blood samples will be analyzed for vitamin D levels (25(OH)D), EPA and DHA levels, and other biochemical parameters. The material will be stored in the study biobank for analyses to explore and explain the main results of the study. These analyses can include both biochemical, immunological, and molecular biology analyses and will be determined based on the results of the investigation.

Biobank

A study-specific biobank for the duration of the study until five years after all participants are dead will be created.
All blood- and other biological samples collected as part of the study will be stored in this biobank.

Questionnaires and consent forms

Participants will already have completed the Koronastudien questionnaires containing questions about risk factors for Covid-19, supplement use, travel history, cancer, cardiovascular disease, and other previous diseases, skin-type, sunlight exposure, and demographic variables). During the study period, it is expected that 1-2 Koronastudien specific follow-up questionnaires will be distributed, and these will be coordinated to reduce the burden of participation. In addition, the following data will be collected from the sub-study participants using electronic forms:

- Screening questionnaire before inclusion (inclusion and exclusion criteria)
- Consent form. The identity of each participant in Koronastudien is known through the consenting procedure using two-factor authentication with Bank ID. The consent form for Transtudien will be sent as a unique link to existing participants, and consenting will be a simple yes or no checkbox at the end of the form without requiring further identification with Bank ID.
- Baseline questionnaire: Diet including an estimate of vitamin D and n-3 LCPUFA intake and other baseline data collection will be coordinated with a follow-up questionnaire in Koronastudien to reduce participant burden.
- Every month: Compliance, use of supplements, side effects, efficacy of blinding, endpoints
- End of study: FFQ (a validated web-based food frequency questionnaire), risk factors for Covid-19 and other relevant diseases, use of supplements, previous conditions, side effects, efficacy of blinding, endpoints
- Follow-up up to two years: Diet, use of supplements, endpoints.

Participants will also be encouraged to report any symptoms of respiratory tract infections and any possible side-effect during the cod liver oil taking period using an electronic questionnaire available to them at all times during the study period.

Dietary questions on vitamin D and n-3 LCPUFA will be based on the FFQ.

Registries

Data for validation of endpoints, previous diseases, and risk factors will be obtained from the following registries (registry, data to be obtained):

- Causes of death: death, and cause of death
- Hospital records: verification of endpoints
- KUHR: visits to GP and cause of visit
- Norwegian Prescription database:, medications
- MSIS (the Mandatory Norwegian Surveillance System for Communicable Diseases): Covid-19 status,- negative and positive SARS-CoV-2 tests.
- The Norwegian Patient Registry (NPR): Hospital admissions and outpatient visits: fractures, health-related events and endpoints
- The patients' general practitioner or treating physician may be contacted for verification of endpoints, adverse effects, and causes of death

- Luftveisdatabasen (Airway Database), Covid-19 status, other PCR and culture verified infections
- Microbiology laboratories, microbial test results not available through Airway Database (HelseNorge.no)
- Other statutory health registries including the Norwegian Pandemic Registry and heart registry
- Folkeregisteret and The Contact and Reservation Registry, contact information, address
- Quality Registries on Covid in Oslo University Hospital, detailed data about risk factors for Covid-19 and outcome of disease

Assessment of dietary and Supplemental Intake Questionnaire

Simple questions about the intake of vitamin D and n-3 LCPUFAs (based on a validated, self-administered semi-quantitative food frequency questionnaire (FFQ)) will be distributed to participants at baseline. Classifying participants by baseline intake of various nutrients will allow us to evaluate whether the study agents' effects vary by such intake. Participants will be asked to complete a complete FFQ.
Questions on the use of non-study supplements or drugs containing vitamin D or EPA+DHA will be asked at baseline and end of the study and on follow-up questionnaires. We will ascertain and analyze intake from food and supplements separately, and from both sources combined.

Follow up

At the end of the intervention, three, six months, 12 and 24 months later, a questionnaire will be sent to participants. The form will be similar to the conventional follow-up questionnaires, collecting information about potential risk factors, major diseases use of medications, and medical history. The additional data will be used to address the duration of any effects seen on the primary endpoints and any side effects of the intervention as well as to explore other health effects of cod liver oil as described in the endpoint section.

Data management

The handling data will be closely connected to the handling of data in Koronastudien, and for data handling purposes, the CLOC study will be treated as a sub-study of Koronastudien. An application to process and store data from the two studies together will be sent to the Data Protection Officer at Oslo University Hospital. Koronastudien has been approved by the Data Protection Officer at Oslo University Hospital in accordance with the European GDPR regulations.

The University of Oslo service for sensitive data (TSD) will be used to collect, store, and analyze data. Additionally, HUNT cloud and LEDIDI Prjcts will be used for analyzing data. The data will be analyzed without any directly personally identifying information using a Study ID instead. The patient list connecting the patient identity with the study ID will be kept in a separate folder in TSD, and the backup will be kept at an encrypted USB data storage device. Deidentified data will be backed up at K:/sensitive, a secure location at the Oslo University Hospital's internal web.

9. Statistical considerations

The detailed statistical analysis plan will be approved by the study steering committee before unblinding.

Statistical Hypotheses

See Sample Size Determination and the statistical analysis plan

Sample Size Determination

The fallback method (https://www.fda.gov/media/102657/download) will be used to correct for testing of multiple primary endpoints.

The total alpha (0.05) will be divided among the endpoints, and a fixed sequence for the testing will be maintained. As the testing sequence progresses, a successful test preserves its assigned alpha as "saved" (unused) alpha that is passed along to the next test in the sequence. This passed-along alpha is added to the assigned alpha of the next endpoint, and the summed alpha is used for testing that endpoint. Thus, as sequential tests are successful, the alpha accumulates for the endpoints later in the sequence; these endpoints are then tested with progressively larger alphas.

Endpoints in testing order with power calculation:

1. Serious Covid-19 (Covid-19 with self-reported dyspnea, self-reported hospitalization, or death). Assigned α=0.018.
   Based on the observations in Koronastudien of a 40% reduction in serious Covid-19 in the group reporting use of cod liver oil, and an expected incidence of 0.25%, a power of 70%, 67,000 participants will have to be included for this endpoint.
2. Covid-19 positive PCR. Assigned α=0.03.
   Based on the observations in Koronastudien of a 20% reduction in Covid-19 incidence in the group reporting use of cod liver oil, and an expected incidence of 1%, a power of 70%, 65,000 participants will have to be included for this endpoint.
3. Frequency of negative SARS-CoV-2 tests (MSIS). Assigned α=0.001.
   Covid tests (SARS-CoV2-2), real time (RT)-PCR, are mostly obtained because of a suspicion of COVID-19. The number of negative covid tests from one week after starting taking cod liver oil/placebo and to the end of the intervention period. This endpoint has been added as an alternative to the Positive PCR or bacterial culture endpoint (secondary endpoint, which is not available at this time).
4. Self-reported airway infection (yes/no). Assigned α=0.001.
   Based on the expected frequency of airway infections in Koronastudien of >30% and as a threshold of clinically interesting reduction of all airway infections of 10%, 23,000 participants will have to be included for this endpoint. The study has a power for this endpoint >95%. 16000 participants in the study will give an 80% power for this endpoint.

Analysis sets

Participants will be assigned to the cod liver oil or placebo group in a 1:1 ratio. The primary endpoints will be calculated using relative risks, Kaplan-Meier plots and Cox regression on the intention to treat (ITT) population with missing data on outcome counting as the negative outcome.

Compliance with cod liver oil taking and power of the study

The power calculation is based on data from Koronastudien and participants reporting taking cod liver oil. We have no data on how often cod liver oil was used by these participants but believe that it is less than once daily on average. Thus, although many participants in the CLOC study will not be fully compliant, we expect that a large majority of participants will have the same level of cod liver oil taking as found in Koronastudien. However, to increase the power, we will attempt to recruit up to 80.000 participants to increase the power of the study.

Interim Analyses

Covid-19-prevalence and power

The power of the study is dramatically influenced by the incidence of Covid-19, and this will be considered when the statistical analysis plan is finalized before unblinding to maximize the scientific output of the study. Thus, the statistical analyses including p-values and testing-order above can be changed if the Covid-19 situation dictates such changes. Any change will be done before unblinding. The time of unblinding can be changed based on the prevalence of Covid-19 to increase the scientific output from the study. No interim analyses will be conducted.

10. Ethics

Risks in the cod liver oil group

Cod liver oil has been used as a supplement for more than 100 years and thus has an excellent safety record. It is explicitly mentioned under the seafood category in official Norwegian dietary advice (https://helsenorge.no/kosthold-og-ernaring/kostrad/spis-fisk-oftere) The main constituents, vitamin D and omega 3 have been used in tens of thousands of participants in well-designed studies with very few side effects [4, 8]. The risk of overdosing is very low because of the relatively large volume of oil that has to be ingested for overdosing.
In a Norwegian study with a similar design as the proposed study also with cod liver oil, it was found that 5 ml of cod liver oil increased the vitamin D level with 17 nmol/liter. This is a moderate increase that will have a very low probability of toxicity, yet still be large enough to treat vitamin D deficiency[9]. To further ensure participants' safety, we will exclude from the trial persons with a history of kidney stones, hypercalcemia, renal failure, cirrhosis, or sarcoidosis or other granulomatous diseases and persons belonging to groups advised to use a vitamin D supplement.

We expect no adverse events related to taking cod liver oil and although possible adverse health effects will be monitored as part of the study, adverse events during the cod liver oil taking period will be expected to be followed up as part of normal care by the relevant health professionals and will not be followed up or reported as part of the study.

Risks in the placebo group

Volunteers older then 75 years old are advised use a vitamin D supplement , according to official dietary advice, and will be excluded from the study in the screening phase and receive an automated message about the official advice if they do not report taking and supplement.

The study aims to identify the health effects of cod liver oil as a supplement to the normal diet of participants not normally using such supplements. Most people have a relatively stable diet over many years, and the study will attempt not to interfere with the diet of participants. We consider that continuing to have the same diet as before during a study period that lasts less than one year poses a negligible risk to participants.
However, the Norwegian dietary recommendations for vitamin D are complicated and depend on how much fish you eat, your age, the season, and your sun exposure. Based on the collected data, participants at high risk for vitamin D or low levels of n2-LCPUFFA will be notified at the end of the study and recommended to discuss their diet with their general practitioner and or get their vitamin D levels and 3n-LCPUFA levels measured.

No measurements of vitamin D or 3n-LCPUFA will be made before unblinding, and this will not be known to the study during the cod liver oil/placebo taking period.

Expected side-effects

Several side-effects have been described for intake of fish oil and low-dose vitamin D, but in practice, very few serious side effects are expected to be found.
For fish oil the following side effects have been described: gastrointestinal (GI) symptoms (stomach upset or pain, nausea, constipation, diarrhea), bleeding (any GI bleed, GI bleeding requiring transfusion, hematuria, easy bruising, epistaxis), skin rash, colds or upper respiratory tract infection, flu-like symptoms, bad taste in the mouth
For vitamin D, the following side effects have been described: GI symptoms as listed above, and hypercalcemia or kidney stones.
Each follow-up questionnaire will contain questions about side-effects.

Importance of study results and generalizability

There is a significant inherent risk in the study that the Covid-19 prevalence becomes much lower than the threshold for detection of any effect or that a Covid-19 cure or vaccine becomes available, making the study results less relevant. However, the primary endpoints of respiratory tract infections will still be of great importance; likewise, the in-depth safety characterization of cod liver oil will be of importance.

Benefits

The main benefit of the study is to identify a new and safe way to prevent Covid-19 or its complications. Furthermore, the study is powered to detect whether cod liver oil can prevent respiratory infections. In addition, the study is well suited to compare positive or negative health effects of cod liver oil In particular, the systematic collection of negative health effects that will be conducted is important to ensure the two year safety of this widely used supplement.

Surveying of risks

A survey of risks of the study will be conducted by the PI and in collaboration with the Department of Research Support, OUH and identified risks will be addressed before the beginning of the cod liver oil taking period.

Ethics summary

In conclusion, the study has a low risk of negative health- or other effects on participants and a high probability of identifying whether cod liver oil can prevent Covid-19 and other respiratory infections. Furthermore, the encouraging preliminary data suggests that the morbidity caused by Covid-19 will be significantly reduced in the cod liver oil group adding to the benefit of the study. Further adding to the benefit is the prospect of collecting high-quality data on the more general health effects of cod liver oil use.

In total, we consider that the benefits of the study far outweigh the risks and disadvantages.

10. 1 Study Administration and Financial Statement

Responsible for the study

Oslo University Hospital is responsible for the study. Arne Søraas, MD, PhD is the PI of the study. The study is a collaboration between OUH, UIO and NIPH.

Steering committee

The PI will appoint a steering committee with representatives from OUH, University of Oslo and the Norwegian Institute of Public Health (NIPH) that will meet regularly during the study period and give

advice to the PI in conducting the study. A patient representative will participate in this committee. At the time of writing the steering committee members are: Arne Søraas, OUH (PI), Professor Stine Ulven, UiO, professor Haakon E. Meyer (UiO, NIPH), professor Anette Hjartåker (UiO), professor Kirsten Bjørklund Holven, (UiO). The user representative is Turid Wøien. Secretary: Mette Istre (OUH).

Monitoring of data quality

The Department of Research Support at Oslo University Hospital will monitor the data quality of the study and randomization.
A statistician from the OUH/UIO statistical research support department will write the statistical analysis plan together with the PI and perform the primary analyses.

All study personal will be obliged to attend to a good clinical practice course. The PI has the Human Subject Research CITI certification.

Financing

The study will be financially supported by Orkla Health, which owns the "Møllers Tran", a widely used cod liver oil brand. The financing will cover most of the expenses for Oslo University Hospital in 2020 and 2021 as well as producing and distributing cod liver oil to the participants and marketing of the study.
The study was initiated by Oslo University Hospital and Koronastudien, who contacted Orkla Health for financing the project.
Orkla Health will not have any influence on the choice of data analyses or publication of study results.

The study aims to attract funding from both private and government sources.

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SAP for Cod Liver Oil for COVID-19 Prevention Study

Contents

Abbreviations

Abbreviation	Full text
BMI	Body mass index
CLOC	Cod Liver Oil for COVID-19 Prevention Study
ITT	Intention to treat
Koronastudien	The Norwegian Corona Cohort
MSIS	Norwegian Surveillance System for Communicable Diseases
PCR	Polymerase chain reaction
SAP	Statistical Analysis Plan

1. Administrative Information

1.1 Title and trial registration

A randomized, parallel-group treatment, participant, investigator, care provider and outcomes assessor masked, two-arm study to assess the effectiveness of cod liver oil compared to placebo in the prevention of COVID-19 and airway infections in healthy adults

Short: Cod Liver Oil for COVID-19 Prevention (CLOC) Study

1.2 SAP version

SAP version 1.0 - 23-November-2021

1.3 Protocol version

Cod Liver Oil for C-19 Prevention Study, protocol version 1.02, November 10, 2021

1.4 SAP revisions

Version No. – Date	Justification	
0.1 – 3-Jun-2021	Initial draft	Pre-analysis
0.9 – 12-Aug-2021	Second draft	Pre-analysis
0.99 – 24-Aug-2021	Draft for approval	Pre-analysis
1.0 – 24-Nov-2021	SAP approved	Pre-analysis

1.5 Roles and responsibility

Trond Haider, Cand. real., Health Economics-Medical Statistics (HE–MS),
Statistician, Author of SAP

Arne Søraas, MD, PhD, Oslo University Hospital,
Department of Microbiology, Section of Research (OUH-MR), Principal Investigator

Sonja Hjellegjerde Brunvoll, PhD, Oslo University Hospital,
Department of Microbiology, Section of Research (OUH-MR), Responsible researcher

Anders Benteson Nygaard, PhD, Oslo University Hospital,
Department of Microbiology, Section of Research (OUH-MR), Data scientist

1.6 Signatures of:

Senior statistician responsible: Trond Haider, Cand. real.

Signature: Trond Haider

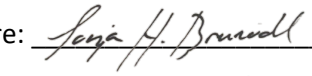
Date signed: 25-NOV-2021

Chief investigator/clinical lead: Arne Søraas, MD, PhD

Signature: A Søraas

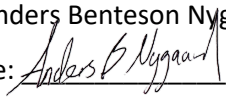
Date signed: November 24, 2021

Responsible researcher: Sonja Hjellegjerde Brunvoll, PhD

Signature: 

Date signed: 25.nov 2021

Data Scientist: Anders Benteson Nygaard, PhD

Signature: 

Date signed: 25.nov 2021

2. Introduction

2.1 Background and rationale

Preliminary evidence from literature and an ongoing study (the Norwegian Corona Cohort, Koronastudien) in our lab suggests that cod liver oil may prevent COVID-19 and complications of COVID-19. In this Cod Liver Oil for COVID-19 Prevention (CLOC) study, we will investigate whether this is actually the case by randomizing volunteers to take cod liver oil or placebo (corn oil) during the winter months of 2020-2021.

2.2 Objectives

Based on the encouraging results from Koronastudien[1] as well as existing evidence from the literature, we aim to investigate whether cod liver oil can prevent COVID-19, serious COVID-19, or other airway infections.

Adverse events will also be presented.

We also aim to explore and confirm already known health effects and possible new health effects in particular rare adverse events associated with cod liver oil use. This will be done during a follow-up period of up to two years after the end of the cod liver oil period.

3. Study Methods

3.1 Trial design

The CLOC study aim to include 80,000 participants that will be randomized in a 1:1 ratio to consume 5 ml cod liver oil or placebo (corn oil) with lemon taste per day for 6 months.

The study was organized as an ancillary study of Koronastudien, a cohort study that aims to identify risk factors associated with the community- and workplace acquisition of COVID-19 virus and which also aims to identify risk factors for the progression of the disease and to understand the virus and the disease itself. Koronastudien has collected extensive electronic questionnaire data using the University of Oslo web-based solution "Nettskjema". Participants of the CLOC study will be a subgroup of participants in

[1] In Koronastudien, the Norwegian Corona Cohort, 140.000 participants have answered a questionnaire about their use of dietary supplements, demographics, airway symptoms, and risk factors for Covid-19. In univariate analyses, it was found that participants using vitamin D and or cod liver oil were associated with a reduced risk of Covid-19 (OR 0.8, p<0.001) and of serious (hospitalized) Covid-19 with hospitalization (OR 0.3, p=0.07).

Koronastudien, and relevant data from these participants will be shared among the studies.

The hypotheses are:

Intake of cod liver oil can prevent COVID-19 disease
Intake of cod liver oil can prevent serious COVID-19
Intake of cod liver oil can prevent other airway infections

These hypotheses will be tested in a triple-blinded randomized placebo-controlled study where 80.000 participants will be assigned to cod liver oil or placebo in a 1:1 ratio.

The safety of cod liver oil will be explored.

Finally, it is a separate aim of the study to identify the mechanisms of action of any health effects seen. These will be explored under another SAP.

3.2 Randomization

Willing and eligible participants will be randomly assigned to one of two treatment groups: 5 ml of cod liver oil x1 per day or placebo together with the first meal each day. Participants will be assigned to the cod liver oil or placebo group in a 1:1 ratio.

Concealment of allocation: Randomization will be conducted at the Department of Research Support, Oslo University Hospital, by personnel not involved in the study. The list of participants with address and treatment assignment will be provided to the packaging company, which will send cod liver oil or placebo for the whole study period to each participant based on that list. The responsible personnel at the packaging company will not be involved in the study, and no personnel involved in the study will have access to this list.

The number of participants to be randomized: In the case of successful recruitment of an excess number of participants, participants belonging to high-risk groups (> 70 years old and dark-skinned) will be prioritized for randomization. The remaining non-randomized participants will be included as an extra control group that will not receive any treatment but will otherwise be followed as the other participants and analysed for the exploratory endpoints.

Previous use of vitamin D

Caucasians using cod liver oil or an equivalent supplement (containing vitamin D) less frequently than 5 days per week can be included in the study. In addition, dark-skinned individuals may be included regardless of previous use of vitamin D (and cod liver oil). We consider the risk of overdosing of vitamin D to be very low in this group and while the group will contribute less to the total power of the study than participants not using such supplements their intake will increase during the study period and they will contribute to the study. Based on data from Koronastudien we expect less than 20-30% such participants.

3.3 Sample size

The fallback method (https://www.fda.gov/media/102657/download) will be used to correct for testing of multiple primary endpoints.

The total alpha (0.05) will be divided among the endpoints, and a fixed sequence for the testing will be maintained. As the testing sequence progresses, a successful test preserves its assigned alpha as “saved” (unused) alpha that is passed along to the next test in the sequence. This passed-along alpha is added to the assigned alpha of the next endpoint, and the summed alpha is used for testing that endpoint. Thus, as sequential

tests are successful, the alpha accumulates for the endpoints later in the sequence; these endpoints are then tested with progressively larger alphas.

Endpoints in testing order with power calculation:

1. Serious COVID-19 (MSIS-confirmed COVID-19 with dyspnoea, hospitalization, or death). (MSIS: Mandatory Norwegian Surveillance System for Communicable Diseases). Assigned α=0.018.

   Based on the observations in Koronastudien of a 40% reduction in serious COVID-19 in the group reporting use of cod liver oil, and an expected incidence of 0.25%, a power of 70%, 67,000 participants will have to be included for this endpoint.

2. COVID-19 positive PCR (MSIS). Assigned α=0.03.

   Based on the observations in Koronastudien of a 20% reduction in COVID-19 incidence in the group reporting use of cod liver oil, and an expected incidence of 1%, a power of 70%, 65,000 participants will have to be included for this endpoint.

3. A negative SARS-CoV-2 test (MSIS). Assigned α=0.001.
   COVID tests (SARS-CoV2-2), real time (RT)-PCR, are mostly obtained because of a suspicion of COVID-19. The number of negative COVID tests from one week after starting taking cod liver oil/placebo and to the end of the intervention period. This endpoint has been added as an alternative to the Positive PCR or bacterial culture endpoint (now a secondary endpoint, as it is not available at this time).
4. Self-reported airway infection. Assigned α=0.001.

   Based on the expected frequency of airway infections in Koronastudien of >30% and as a threshold of clinically interesting reduction of all airway infections of 10%, 23,000 participants will have to be included for this endpoint. The study has a power for this endpoint >95%. 16,000 participants in the study will give an 80% power for this endpoint.

The power of the study is dramatically influenced by the incidence of COVID-19, and this will be considered when the statistical analysis plan is finalized before unblinding to maximize the scientific output of the study. Thus, the statistical analyses including p-values and testing-order above can be changed if the COVID-19 situation dictates such changes. Any change will be done before unblinding. The time of unblinding can be changed based on the prevalence of COVID-19 to increase the scientific output from the study.

3.4 Framework

The background for the study is that data suggest that cod liver oil may prevent COVID-19 and complications of COVID-19. Hence, this is a superiority study, placebo-controlled, blinded and randomised, designed to show that cod liver oil has a positive effect on COVID-19 and complications of COVID-19, compared to corn oil, the placebo.

3.5 Statistical interim analyses and stopping guidance

No interim analyses were planned in this study. The study's duration has been specified to last during the winter months of 2020–2021, with a duration from 1–6+ months for the participants.

3.6 Timing of final analysis

All primary variables will be analysed after ending the intervention part of the present study. Analyses of the four primary variables will be conducted immediately pursuant to

the approval of this SAP. Further analysis of the secondary variables will be specified in another SAP.

3.7 Timing of outcome assessments

Outcome assessment

Time points at which the outcomes are measured including visit "windows"

4. Statistical Principles

4.1 Confidence intervals and *P* values

An overall significance level of 0.05 is used for the composite primary endpoints and are tested in the specified order as seen in section 3.3, above. To control the overall significance level pertaining to the primary hypotheses, the fallback method for alpha spending is used for the statistical analyses of relative risk comparing the two randomisation groups, Cod liver oil and Corn oil. If the first analysis results in significant results, i.e., p≤0.018, according to section 3.3, the second null-hypothesis can be tested at a significance level of 0.018+0.030=0.048. If the first null -hypothesis is not rejected, the second is tested at the stated significance level of 0.03. Each following null hypothesis to be tested has a significance level of its stated level plus the sum of the levels of previous tests that result in a significant result. Supplementary analyses, such as regression analyses, will not be part of the fallback method, as these are expected to be highly correlated to the primary analyses. Confidence interval and p-values will be provided for all variables tested statistically.

4.2 Adherence and protocol deviations

The Intention-to-treat (ITT) population will be used for statistical testing of the primary variables. Hence, anyone who received bottles of cod liver/corn oil will participate in the primary variables' analyses. As a number of bottle shipments were for several reasons returned to sender, such as wrong address, address in another country or did not collect the bottles at the post office despite several urgings, the ITT population is defined as those who had the choice to start taking cod liver/corn oil. Primary variable statistics will also be presented for all who were sent cod liver/corn oils. Participants with missing data on primary variables will be considered as having a negative outcome. Supplementary analyses will be conducted on participants who have reported on the primary variables and on taking oil at given fractions, to be specified when analysing the data, of "the last fortnight".

5. Trial Population

5.1 Screening data

Data from the first reported questionnaire will be considered as baseline wherever such values are considered necessary.

5.2 Eligibility

All participants invited to this study are considered eligible.

5.3 Recruitment

Information to be included in the CONSORT flow diagram.

5.4 Withdrawal/follow-up

The level of reported oil consumption per time unit and overall will be presented. The number of participants with last reported data will be presented for each data collection time-point.

5.5 Baseline patient characteristics

The following baseline variables[2] will be presented for each treatment group and overall:

- Age group
- Gender
- Weight
- Height
- BMI
- Occupational status
- Education level
- Household income
- Household count
- Children living at home
- Smoking habits
- Chronic disease (Yes/No)
- Parents ethnic origin
- Skin type
- Sun exposure (July to October 2020)
- Dietary intake:
    - Vitamin D supplement
    - Omega-3 supplement
    - Cod liver oil
    - Fatty fish intake

Follow-up variables:

- Compliance
- Airways infections
- SARS-CoV-2-tested (negative and positive)
- Dyspnoea (among COVID positive participants)
- Side effects (counts (%)), self-reported free-text fields

Lab

- Vitamin D (baseline and change from baseline)
- Omega-3 index (baseline and change from baseline)
- Baseline serology

MSIS data:

- Positive and negative test results

For continuous baseline variables N, mean, standard deviation, median, minima and maxima will be presented. For categorical variables, N and Per cent will be presented for each oil group.

[2] The specific SAS variable names in the received data set are presented in Appendix 1.

6. Analysis

6.1 Outcome definitions

Primary variables:

- First primary: Serious COVID-19 (MSIS-confirmed COVID-19 with dyspnoea, hospitalisation, or death)
- Second primary: COVID-19 defined by positive PCR obtained from MSIS
- Third primary: A negative SARS-CoV-2 test (MSIS).
- Fourth primary: Self-reported airways infection

The first incidence of report of any of the above primary variables will be used in the analyses. The specified order will be used for the fallback analyses. The values of all variables will be Yes/No to the condition together with time from start of oil consumption to first reporting of the condition, i.e. Yes. Those not reporting a Yes answer, the last reported time will be used as censoring time. The date of oil-consumption starts to the date of reporting of a Yes will be converted to number of days from the first to the second date.

The primary analysis set is the defined ITT sample with missing data on outcome counting as the negative outcome.

Compliance

For sensitivity analyses on compliance, we will define compliant participants as those having taken CLO for at least 2 months. We will also analyse participants based on volume CLO taken (more than 250 ml).

6.2 Analysis methods

The first, second and fourth primary variables will be analysed for relative risk (risk ratio) of acquiring a condition using cod liver oil versus corn oil using the Wald test[3]. Time to first occurrence of the primary variables will be plotted using the Kaplan-Meier approach. The third primary variable will be compared for the two treatment groups tested using study duration-adjusted counts. If the use of student's t-test cannot be used due to underlying assumptions not holding up, a median test will be used. If appropriate, the Cox proportional hazard regression will be used to assess the effect of the outcome of the above specified baseline variables on time to occurrence of the primary variables. Otherwise, logistic regression on the occurrence of outcome will be undertaken with the same explanatory variables. The explanatory variables to be included in the main regression analyses are:

- Age at CLOC screening
- Gender
- BMI
- Occupational status (employed/not employed?)
- Children at home (Y/N)
- Chronic disease (Y/N ≥1 chronic diseases)
- Dietary intake (Y/N)

[3] © SAS Institute Inc. https://documentation.sas.com/doc/no/pgmsascdc/v_016/statug/statug_freq_details70.htm, 18-Aug-2021

    - Cod liver oil
    - Vitamin D
    - Omega 3
    - Fish consumers
- Present smoker (Y/N)

Other variables will be included in ad hoc/exploratory analyses.

The sample size in this study is so large that normal assumptions are likely to be valid. If this should not be appropriate for specific variables, appropriate non-parametric alternatives will be used. Should the assumptions to use Cox proportional hazard model not be satisfied, an alternative approach is logistic regression. The assumptions for methods used will be assessed. Should they be violated and not rectified by the sample size, alternative approaches will be used.

Sensitivity analyses will be conducted by including subsets of the study sample based on compliance. Other baseline variables may also be proposed as basis for ad hoc sensitivity analyses. Overdispersion will be considered for models where that can be an issue.

Further ad hoc subgroup analyses may be performed based on the findings of the primary analyses.

6.3 Missing data

The primary variables will be assumed to be negative, A "No" answer, if no positive answer is reported.

6.4 Harms

Adverse events will be presented for each treatment group, at each reporting time and accumulated over the whole study duration from start of oil consumption.

Data will be summarized in tables of means and medians for continuous variables and tables of counts for discrete variables. Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis

6.5 Statistical software

SAS© version 9.4 will be used to analyse the data.

6.6 References

1. Study protocol: Arne Søraas – Principal Investigator, *Protocol for the Cod Liver Oil for Covid-19 Prevention study.* Oslo University Hospital, Department of Microbiology, Section of Research, Oslo, Norway

Appendix 1: SAS variable names used in the received data set

The table below presents the SAS variable names as they appear in the original SAS data set received.

Variables	SAS variable names
Age group	
Gender	
Weight	
Height	
BMI	
Occupational status	
Education level	
Household income	
Household count	
Children living at home	
Smoking habits	
Chronic disease (Yes/No)	
Parents ethnic origin	
Skin type	
Sun exposure (July to October 2020)	
Dietary intake (Yes/No):	
Vitamin D supplement	
Omega-3 supplement	
Cod liver oil	
Fatty fish intake	
Compliance	
Airways infections	
SARS-CoV-2-tested	
Self-reported free-text side effects	
Laboratory measurements:	
Vitamin D	
Omega-3 index	
Baseline serology	

Primary variables:	
1. Serious COVID-19 (MSIS-confirmed COVID-19 with Dyspnoea, hospitalisation, or death)	*CLOC_primary_1_severe_c19*
2. COVID-19 defined by positive PCR obtained from MSIS	*CLOC_primary_2_msis_status*
3. A negative MSIS SARS-CoV-2 test	*CLOC_primary_3_negative_tests*
4. Self-reported airways infection	*CLOC_primary_4_selfrep_airway*

Description of the calculation of the four primary variables

- **First primary:** Serious COVID
  - *CLOC_primary_1_severe_c19*
    - Created by merging *deriv_sym_dyspnea_post_cov_yn_ever* and *deriv_hosp_post_cov_yn_ever (see description below)*
    - 1 = ever answered yes for dysp or hosp
    - 0 = only answered no for dysp or hosp
    - 999 = has filled out forms, has not answered for dysp or hosp question
    - NA = has not filled out forms / not tested positive (second primary)
  - Only participants fulfilling the criteria for the second primary, will be included in this analysis.
  - Dyspnoea criteria
    - Variable: *deriv_sym_dyspnea_post_cov_yn_ever*
      - Answered dyspnoea in forms (R1-R6, E2, Q1) submitted after positive cov test (MSIS)
      - 1 = ever answered yes in any form
      - 0 = only answered no in any form
      - 999 = has filled out form, has not answered dypnoea question
      - NA = has not filled out form
  - Hospitalized criteria
    - Variable: *deriv_hosp_post_cov_yn_ever*
      - Answered hospitalized because of COVID in forms (B1, B2, R1-R6, E2) submitted after positive cov test (MSIS)
      - 1 = ever answered yes in any form
      - 0 = only answered no in any form
      - 999 = has filled out form, has not answered hospitalized question
      - NA = has not filled out form
  - Death criteria
    - Participant registered as dead/deceased in the National Population Register after a positive cov test (MSIS), but only if the death was related to COVID-19 based on hospital records or information from relatives.

- **Second primary:** New MSIS positive
  - *CLOC_primary_2_msis_status*

        - Created from *MSIS_CLOC_test_status*
        - 1 = tested positive for the first time during **CLOC participation period**
        - 2 = only tested negative during **CLOC participation period** (never positive)
        - 3 = untested during **CLOC participation period** (never positive)
    - MSIS criteria
        - Variable: *MSIS_CLOC_test_status*
            - 1 = tested positive for the first time during CLOC
            - 2 = only tested neg during CLOC (never positive)
        - *Variables obtained through MSIS (translated): "Test date" and "Test result"*
        - Variable to be analyzed as second primary endpoint identifying only tests registered during the **CLOC participation period** (defined as period from start of cod liver oil/placebo consumption (*deriv_Date_CLO_start_corr*) to June 2, 2021).

- **Third primary:** Negative test
    - *CLOC_primary_3_negative_tests*
        - Generated from *MSIS_CLOC_TotalTests_neg*
        - Sum of total negative tests registered during the **CLOC participation period**.
        - 0 if no tests registered
    - Negative test criteria
        - Variable: *MSIS_CLOC_TotalTests_neg*
            - Sum of total negative tests registered during the **CLOC participation period**.
    - Supplementary variables
        - *MSIS_CLOC_FirstNegative*
            - Date of first negative test registered during the **CLOC participation period**.
        - *MSIS_CLOC_LastNegative*
            - Date of last negative test registered during the **CLOC participation period**.

- **Forth primary:** Self-reported airway infections
    - *CLOC_primary_4_selfrep_airway*
        - *Generated from*
            - 1 = ever answered yes in any form
            - 0 = only answered no in any form
            - 999 = has filled out form, has not answered dypnoea question
            - NA = has not filled out form

    - Self-reported airway infections criteria
        - Variable: *deriv_respinf_report_yn_ever*
            - Answered question *has had respiratory infection since last cloc report* in any CLOC questionnaire (R1-R6)
                - 1 = ever answered yes in any form
                - 0 = only answered no in any form
                - 999 = has filled out form, has not answered dypnoea question
                - NA = has not filled out form
    - Supplementary variable
        - *deriv_respinf_count report_sum*

    - Number of respiratory infections reported
- *R**x**_Date_respiratoryinfection**x**_sym_start_report*
    - Date of each infection reported in each report form