Study protocol

Tobacco use and uptake of COVID-19 vaccinations in Finland: a general population study

Start date: March 29, 2022
Latest revision: June 15, 2022

Version 1.0
Revision history: this protocol has not been revised

Sebastián Peña,[1] Laura Kestilä,[1] Maria Rosaria Galanti,[2,3] Ahmed Nabil Shaaban,[2] Ida Henriette Caspersen,[4] Per Magnus, [4] Hanna Nohynek,[1] Suvi Parikka,[1] Sakari Karvonen[1]

Affiliations:

1. Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Mannerheimintie 166, 00271, Helsinki, Finland
2. Department of Global Public Health, Karolinska Institutet, Sweden
3. Centre for Epidemiology and Community Medicine, Stockholm Region

Collaborators:
Karolinska Institutet
Norwegian Institute of Public Health

Funding:
The Tobrisk-CoV study is funded by NordForsk (project number 105544)

Background

The COVID-19 pandemic continues to spread worldwide, resulting in more than 541 million cases and more than 6.3 million deaths worldwide by June 15, 2022.[1] Rapid viral dissemination in many parts of the world has led to the emergence of several variants of concern, with greater transmissibility and severity.[2,3]

During 2020, many countries resorted to strict public health and social measures as means to curb the pandemic, including large-scale lockdowns, closure of schools and public spaces, travelling restrictions and face masks mandates. In 2021, most high-income countries began rolling out COVID-19 vaccinations, with the promise of reducing incident COVID-19 infections and preventing hospitalizations and deaths. Achieving high vaccination coverage is crucial for several reasons: (i) to reduce the number of new COVID-19 cases,[4] (ii) to diminish selective pressures leading to the emergence of new variants of concern,[5] (iii) to prevent severe COVID-19 outcomes, such as hospitalizations and deaths,[6] and (iv) to potentially reduce the risk of post-acute COVID-19 symptoms.[7]

Smokers are at higher risk of COVID-19 hospitalizations and deaths[8] and might thus benefit greatly from high vaccination coverage. However, evidence suggests that they may be less likely to be vaccinated, as smokers are less likely to adhere to preventive measures in general and have lower adherence to other vaccines.[9,10] Reports of a protective role of smoking on the risk of COVID-19 infection might have also reduced the perceived risks from being infected.[11] Evidence regarding tobacco use and COVID-19 vaccine hesitancy is mixed. Some studies have shown greater mistrust in COVID-19 vaccine benefits[11-14] and greater vaccine hesitancy and lower vaccine acceptance compared to non-smokers,[11,15,16] while other studies have reported no differences by smoking status or lower levels of vaccine hesitancy in smokers compared to non-smokers.[17-20]

Vaccine uptake, however, is a dynamic process not only influenced by trust and risk perception, but by convenience factors related to physical and geographical availability, affordability, ability to understand and appeal of immunisation services.[21] To our knowledge, two studies from convenience samples in Singapore and Palestine have examined vaccination uptake by smoking status.[22,23] Both studies showed that smokers had higher odds of being vaccinated.[22,23] However, these studies are not representative of the general population and relied on self-reported vaccination status, resulting in a higher risk of selection and information bias. Spacing between vaccine doses is also relevant, as a growing body of literature suggests that smokers develop a weaker immune response to COVID-19 vaccines.[24]

Finland developed a national COVID-19 vaccination strategy and the vaccine rollout started on December 27, 2020. Vaccinations started with priority groups (health and social care personnel and people at high risk of severe COVID-19) but eventually were expanded to the whole population aged 5 and over.[25] COVID-19 vaccines are provided free of charge and delivered nationwide by each municipality. Finland has administered primarily mRNA vaccines (Cominarty and Spikevax).[25] Vaccination coverage in the Finnish population aged 18 and older has reached 89.7% for the first dose, 87.6% for the second dose and 65.1% for the booster dose by June 14, 2022.[26]

In this study, we will examine the association between tobacco use and COVID-19 vaccine uptake and between-dose spacing. Given conflicting results of previous studies, we expect to observe an association between tobacco use and vaccination uptake and dose-spacing, but the direction of the effect is unclear. We will expand current knowledge by examining two forms of tobacco use in Finland -smoking and smokeless tobacco use (snus)- and by analysing the spacing between vaccine doses. We will use data from nationally representative surveys in Finland linked to vaccination registries, which reduces the risk of selection and information bias.

Methods

The study protocol has been written in close accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies.[27]

Study design

The study design is a cohort study of nationally representative health surveys linked to COVID-19 vaccination data derived from the Finnish National Vaccination Register, using a unique personal identification number assigned to all residents in Finland.

Setting and participants

We will use data from two FinSote Surveys, which are cross-sectional population health surveys in Finland.

Participants in the FinSote 2018 Survey were adults aged 20 years and over derived from the Population Register of Statistics Finland, which comprises all residents in Finland. This sampling frame includes people living in institutions and military conscripts.[28] The survey

was based on stratified random sampling, one stratum for each 19 counties. In 2017, 3300 people were invited to participate from 18 research areas (2300 adults aged 20-74 and 1000 adults aged 75+, total sample size 59400). Data was collected between October 2, 2017, and March 3, 2018. Participants received a self-administered questionnaire in Finnish, Swedish, English or Russian, which could be returned on paper or filled in electronically. The participation rate was 45%, resulting in a total of 26422 participants.[28] Participants were asked for consent for registry linkage, resulting in an analytical sample of 14736 subjects.

Participants in the FinSote 2020 Survey were adults aged 20 and over derived from the Digital and Population Data Services Registry, created in Jan 2020 after the merge between the Population Register of Statistics Finland and local register offices.[29] This sampling frame includes all residents in Finland. The survey was based on a stratified random sample of 22 regions (2000 adults aged 20-74, 800 adults aged 75+, total sample size 61600). Data collection started on September 14, 2020, and finished on February 8, 2021. Participants received a self-administered questionnaire in Finnish, Swedish, English or Russian, which could be returned on paper or filled in electronically. The analytical sample is 28199 participants, with a participation rate of 46%. In 2020, consent to linkage was included in the overall consent, and as a result, we were able to link all participants in the analytical sample.

We will link data from FinSote 2018 and 2020 surveys to the Finnish National Vaccination Register maintained by the Finnish Institute for Health and Welfare using a unique identifier assigned to all residents in Finland. The follow-up will be between December 27, 2020 (date of the first COVID-19 vaccination in the country) until May 31, 2022 or the latest available date.

Outcomes

Our primary outcome will be the vaccination uptake of at least two doses of a COVID-19 vaccine. We will examine four secondary outcomes:

(i) vaccination uptake of at least one dose of a COVID-19 vaccine,

(ii) vaccination uptake of the complete COVID-19 vaccination scheme (two doses and a booster dose),

(iii) proportion of participants with more than 7 months between the first and second COVID-19 dose, and

(iv) proportion of participants with more than 7 months between second dose and booster dose.

We will include any approved COVID-19 vaccination in Finland by the latest available date (i.e. April 29, 2022):[30] COVID-19 mRNA vaccines (Cominarty and Spikevax), recombinant vaccines (Vaxzevria, COVID-19 vaccine Janssen, COVISHIELD, Nuvaxovid, COVOVAX), and inactivated vaccines (BIBP/Sinopharm, COVAXIN, Coronavac). Participants who have received the COVID-19 vaccine Janssen would be excluded from analyses on the second dose, as the vaccine only requires a single dose.

Exposures

We will examine two forms of tobacco use: smoking and smokeless tobacco (snus) use. We will assess smoking status with the following question: Do you smoke currently (cigarettes, cigars or pipe)? (a) yes, daily, (b) occasionally, (c) not at all, (d) I have never smoked. We will create a categorical variable with the following categories: never smokers, former smokers, current occasional smokers and current daily smokers.

We will assess snus use with the following question: Do you currently use any of the following products? Snus (Swedish type moist stuff) (a) yes, daily, (b) occasionally, (c) not at all, (d) I have never used. We will create a categorical variable with the following categories: never users, former users, current users (daily and occasional combined). Data on smoking status is available for all participants, while data on snus use was available for participants aged 20-74 years old.

Potential confounders

We will adjust for several potential sociodemographic confounders: age, sex, marital status, educational tertile, and participation in social activities. All variables will be analysed at baseline. We will define marital status as those married or in a registered relationship or cohabiting versus those separated or divorced, widowed or single. We will calculate educational tertiles for each survey year using the years of education reported in the question "How many years altogether have you attended school or studied full time?". We will analyse participants' mother tongue using data from national registries and will categorise it into three categories: Finnish, Swedish and other. We will measure participation in social activities with a question about participation in the activities of any club, association, hobby group or religious or spiritual community. We will categorise participation into the following: no participation, occasional and active.

Effect modifiers

We will examine potential effect modification by reporting stratified results by age (as a categorical variable), sex and educational level.

Data sources and measurement

Data sources and measurements for all variables were described above. More details on the exact variables can be found in the Supplementary Appendix.

Bias

Confounding bias

We will reduce the risk of confounding by adjusting for potential confounders that causally precede the exposure and are associated with the outcome. We build a directed acyclic graph to guide the identification of potential confounders and mediators (Figure 1). Adjusting for mediators can result in an underestimation of the association and potentially introduce M-bias (a type of collider bias).[31,32]

Selection bias

FinSote surveys 2018 and 2020 are based on a stratified random sample design that represents the Finnish population. However, non-participation in the survey could potentially introduce nonresponse bias if participants are systematically different from non-participants. For this purpose, we will take into account the complex survey design in all analyses and use the inverse probability weights (IPW) created by the Finnish Institute for Health and Welfare using a model with register-based data for the whole sample on age, sex, marital status, educational level, mother tongue and place of residence. The IPW method allows correcting for survey non-participation and the weighting factor of each participant is a combination of the inverse of the participation probability and the sampling probability. Hence, the set of weighted coefficients represents the Finnish population.[33]

Information bias

The risk of information bias from measurement error of the exposure and confounders is inherent to most population health surveys. However, our data is almost entirely collected before assessment of the outcome, reducing the possibility that the exposure is affected by the occurrence of the outcome (i.e. that COVID-19 vaccination affects tobacco use). COVID-19 vaccination in Finland started on December 27, 2020, with a focus on health and residential care workers. The number of doses available in the first months was limited, so it is unlikely that participants from FinSote 2020 received the vaccination before the data collection. As sensitivity analyses, we will carry out the same analyses but excluding participants who have received a vaccination dose prior to February 8, 2021, when the data

collection of FinSote 2020 ended. In addition, smoking status was collected relatively close to the COVID-19 vaccination, reducing (although not excluding it completely) the risk of exposure misclassification.

The COVID-19 vaccination has been implemented nationally by public providers, meaning that all COVID-19 vaccines provided have been registered in the Finnish National Vaccination Register. We estimate the risk of loss to follow-up and information bias of the outcome to be close to zero.

Study size

The sample size was determined by the available data from FinSote surveys 2018 and 2020. We consider it not necessary to provide a sample size calculation.

Quantitative variables

We described the categorisation of exposures and confounders above. We modelled age as a continuous variable and tested non-linearity by comparing the linear model with penalised smoothing splines using a likelihood ratio test.[34] The variable years of education was modelled as categorical to be able to account for secular changes in years of education during the study years. In other words, educational attainment increases over time and it is therefore more appropriate to calculate the educational attainment within each survey wave.

Statistical methods

We will use Poisson regression with robust standard errors to estimate the relative risk of confirmed COVID-19 cases. We will fit the following Poisson model:

$$(1) \qquad log\ \mu_i = \beta_0 + \beta_1 S_i + \beta_x X_i^* + \rho_1 R_a$$

where i denotes the individual, $\beta_0$is the intercept; $\beta_1$is the coefficient of interest for exposure to tobacco S; a vector of covariates X^* (i.e., sex, age, marital status, years of education, mother tongue and participation in social activities); and fixed effects $\rho_1 R_a$ for wellbeing area a. We will report the exponentiated coefficient as the relative risk estimate for unadjusted and adjusted models with their corresponding 95% confidence intervals.

We will examine non-linearity between age and the outcome by comparing the linear model with penalised smoothing splines[34] using a likelihood ratio test with the Wald method.[35] We

will use the model with splines if it performs better than the linear model, using a p-value of 0.05 as the threshold for this decision.

We will examine potential effect modification by reporting stratified analyses by age, sex and educational level. If there are noticable differences, we will test for multiplicative interactions between tobacco use and sex, age and educational level by including an interaction term in equation 1. We will introduce the interaction terms one by one for each of the examined interactions. We will use a likelihood ratio test to compare the model with and without the interaction. A p-value lower than 0.05 in the likelihood ratio test will be used as an indication of the presence of an interaction. If there is evidence of an statistically significant interaction, we will include the interaction term in the final model.

Our primary method to handle missing data will be multiple imputation, given that a missing at random assumption is the most likely in our data. We will examine patterns of missing data and use multiple imputation using chained equations (MICE). This procedure will be combined with the survey design tools to take the complex sampling design into account.

In sensitivity analyses, we will report estimates using complete case analyses (i.e. taking only the complex sampling design into account). We will also report the same estimates as the main analyses, but restricting the follow-up time to when vaccination coverage reached 60% and 80%. This will allow us to understand whether these associations changed over time and also provide estimates that might be comparable to countries with lower vaccination coverage, thus increasing the external validity of our estimates.

We will analyse the data using R version 4.1.1 and include the statistical code as a Supplementary Appendix.

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