Typical COVID-19 symptoms are inversely associated with statin medication: cross-sectional digital study in Lower Saxony, Germany Results of the first German Surveillance Study for COVID-19

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Abstract

Background: As the Coronavirus pandemic continues to spread across the globe, the world continues in its search for a medication to cure, or attenuate, the symptoms of COVID-19 infection.
It would be desirable, and fortuitous, to identify such a medication already in use for another condition, and whose side effect profile and safety data are already known and approved.

Objective: To design an ‘app’ with the purpose of tracking the incidence of typical COVID-19 symptoms in the population under study, and to detect possible associations between symptom severity and pre-existing medical conditions or medication therapies.

Methods: Between early April and late July 2020, 3990 people in Lower Saxony, Germany, participated in an online symptom tracker application, ‘covid-nein-danke.de’. The questionnaire contained items on typical COVID-19 symptoms, age range, gender, work in patient-facing healthcare, community life, postal code, previous illnesses, permanent medication, vaccination status, and results of PCR and antibody test for COVID-19, and COVID-19 treatment if performed.

Results: Analysis of the results have demonstrated a statistically significant relationship between a lower incidence of typical COVID-19 symptoms and concomitant statin therapy and, to a lesser extent, with antihypertensive therapy. Defining COVID-19 infection by restrictive symptom criteria (4 out of 7 symptoms) the association was found solely for statins with a statistically significance (OR 0,28 (0,1 - 0,78)). These findings are in line with recent studies.

Conclusions: People taking statin medication may not present with the typical COVID-19 symptoms. This relates especially to the symptoms of “sore throat”, “headache”, and “dry cough”. The results of this study should be incorporated into all ‘symptoms-based ‘surveillance and decision-making protocols in respect to COVID-19. Furthermore, we conclude with the assumption that people taking statin therapy may be more likely to have an asymptomatic COVID-19 infection, in which case they may be at an increased risk of transmitting it unknowingly.
Whether statin therapy has a beneficial effect in combating COVID-19 infection should be investigated by further study. Our ongoing digital surveillance study will continue to investigate the possible preventative role of statin therapy in symptomatic SARS-CoV-2 infection. Currently the results should not be misinterpreted as a recommendation to take statins for prevention or treatment of COVID-19. Clinical Trial: German Clinical Trial Register No. DRKS000022185, WHO International Clinical Trials Registry Platform U1111-1252-6946.

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(Trial Registration)

German Clinical Trial Register No. DRKS000022185, WHO International Clinical Trials Registry Platform U1111-1252-6946.

Keywords:
Covid-19; SARS-CoV-2; statins; antihypertensives; surveillance; hydroxymethyl-glutaryl-coenzyme A reductase inhibitors; online survey.

Introduction

More than eight months since the SARS-CoV-2 2019 infection was first detected in Wuhan, China, the worldwide incidence is still increasing [1]. Despite widespread research efforts, no curative therapies for treating, what has been named coronavirus disease, COVID-19, have been established, and a safe vaccination is unlikely to be available before 2021. In Germany, the first known infection with SARS-CoV-2 was recorded at the end of January 2020; a peak of new infections was noted during the following March and April [2,3].
The first epidemiological studies of the disease demonstrated that age and preexisting medical conditions, in particular cardiopulmonary diseases, are associated with a high fatality rate in patients hospitalized because of COVID-19 [4]. However, it remains unclear why some people within the risk groups suffer severely from the infection, while others do not, and whether the early findings from China can be replicated in populations across the world. Secondly, the role of medication, as well as vaccination status, in preventing patients infected with COVID-19 from becoming severely ill is under debate [5,6]. Thirdly, there was insufficient surveillance of the disease when the infection spread to Germany. Surveillance of the disease by PCR results was initiated by the Robert-Koch-Institution in Germany. However, due to limited test resources only a small cohort of people were included during the first infection wave. Furthermore, no surveillance based on typical COVID-19 symptoms had been established in Germany at that time.
Many management decisions and recommendations in respect to COVID-19 are based on the presence of typical symptoms. For instance, screening for suspected COVID-19 patients, an indication algorithm for PCR-testing and the recommendations for self-isolation. In addition, regional symptom tracking is used to detect a rising infection wave [7,8]. In several previous studies the typical symptoms were numerically gathered. However, the value of those symptoms is discussed controversially [9].
To address the research challenges as described above and test pilot a symptom-based regional surveillance system, the decision was made to combine an online symptom-tracker application with the elicitation of medical data which might impact on the severity of COVID-19 infection. The survey started at the end of March 2020 as a pilot project in a region of lower Saxony in Germany. At the same time, a symptom tracker application was distributed in the UK [7]. Later on, symptom trackers were instigated successfully in more areas [10].
The aim of the current study was to evaluate the influence of medication on typical COVID-19 symptoms, using data from our surveillance survey.

Methods

Data collection
Data was collected using an online questionnaire which was implemented by the browser-based application ‘covid-nein-danke.de’ which was developed between 10th March and 27th of

March 2020 by two of the authors (S.L., D.U.). The first data was entered by volunteers on the 2nd of April 2020.
The questionnaires can be completed using a computer or an internet enabled mobile phone or tablet. Due to data protection requirements the application was constructed as a browser-based application without the need for downloading a program. Technically, the study is based on a single page application written in JavaScript and a high scalable cloud. To address estimated high data volumes and make the questionnaire adaptable for changes, a NoSQL database was used.
Under the URL "covid-nein-danke.de" the survey is described. Once a potential participant has agreed to the data privacy policy according to European General Data Protection Regulation (DS-GVO) and confirmed that they are over 18 years old, they are guided through the questionnaire (as described below). The overall time taken to complete the survey is around three to 5 minutes. After finishing the survey, a 7-digit code is randomly created and given to the user for follow-up surveys. The application works without user "tracking", without gathering an email-address, and without IP-address storage, or other details allowing identification of participants. Data collection is therefore completely anonymous.

Questionnaire items

The questionnaire contained items on age range, gender, work in patient-facing healthcare, community life, postal code, previous illnesses, permanent medication and vaccination status. It included the results of any COVID-19 PCR or antibody tests and any COVID-19 treatment. More specifically, the following symptoms were assessed: "dry cough", "increased temperature or fever (>37.5 degrees Centigrade)", "shortness of breath (new occurrence)", "muscle or joint pain (new occurrence)", "sore throat", "headache", "loss of smell or taste (new occurrence). The participant confirmed "yes" or "no" for each question.
Participants were asked; "Do you take regular medication?". When confirming with a "yes", the following medication could be chosen by the use of a "yes-no" slider: Cholesterol-lowering medication (e.g. simvastatin), NSAID (ibuprofen, diclofenac), thyroid medication (e.g. levothyroxine), omeprazole/pantoprazole, metamizole, antihypertensives, furosemide or HCT, cortisone, DMARD including methotrexate, biologics, hydroxychloroquine, antihistamines.
If "antihypertensives" were chosen, participants were asked to choose from the alternatives, Ramipril, Beta-Blockers Metoprolol, Bisoprolol, Amlodipine. Further information on medications not explicitly requested could be given in a free text field.

Acquisition of Volunteers

In the pilot study, a population in the district of Gifhorn in the federal German state of Lower Saxony was motivated to participate by regional newspaper articles, you-tube video, social media and regional broadcast.

Investigated population

From 2nd of April to 20th of July 3990 people participated in the online survey. From these, 3654 people were evaluated. Data from 336 people were deleted due to incomplete data entry.

Statistics

The raw data was transformed from a JSON -Format to a rational data format for further evaluation. The data analysis and graphical output for this paper were generated using SAS/STAT® Software. To investigate associations between typical COVID-19 symptoms and

medical characteristics, we ran logistic regression (logit model) models. Odds Ratio (OR) estimates with corresponding 95% confidence intervals (CIs) were computed for each medication and each symptom. Based on the assumption that the presence of 4 out of 7 symptoms equates to COVID-19 infection, the association of COVID-19 infection with concomitant medication intake was calculated in the same manner.

Ethics

The online study was approved by the ethical committee of the Otto-von-Guericke-University Magdeburg (Ref. 65-20). The study is registered in the German Clinical Trial Register with the No. DRKS000022185 and WHO International Clinical Trials Registry Platform U1111-1252-6946.

Results

Epidemiological data

The mean age range of the cohort was 51.1 years, with a peak at 55 years for both, female and male participants. Specific gender mean ages were 48.9 for females, 54.1 for males, and 47.5 for third gender. Females participated more often than males (Figure 1). The average age of the official epidemiological data of the local authorities for the observed district was almost the same (51.8 years versus 51.1 years). However, it was lower for females and higher for males (Table 1). As in the cohort of the present survey, the peak age was between 50 and 59 years according to official statements.

Figure 1: Age-Range-Distribution. Gender O=male; 1=female; 2=3rd gender

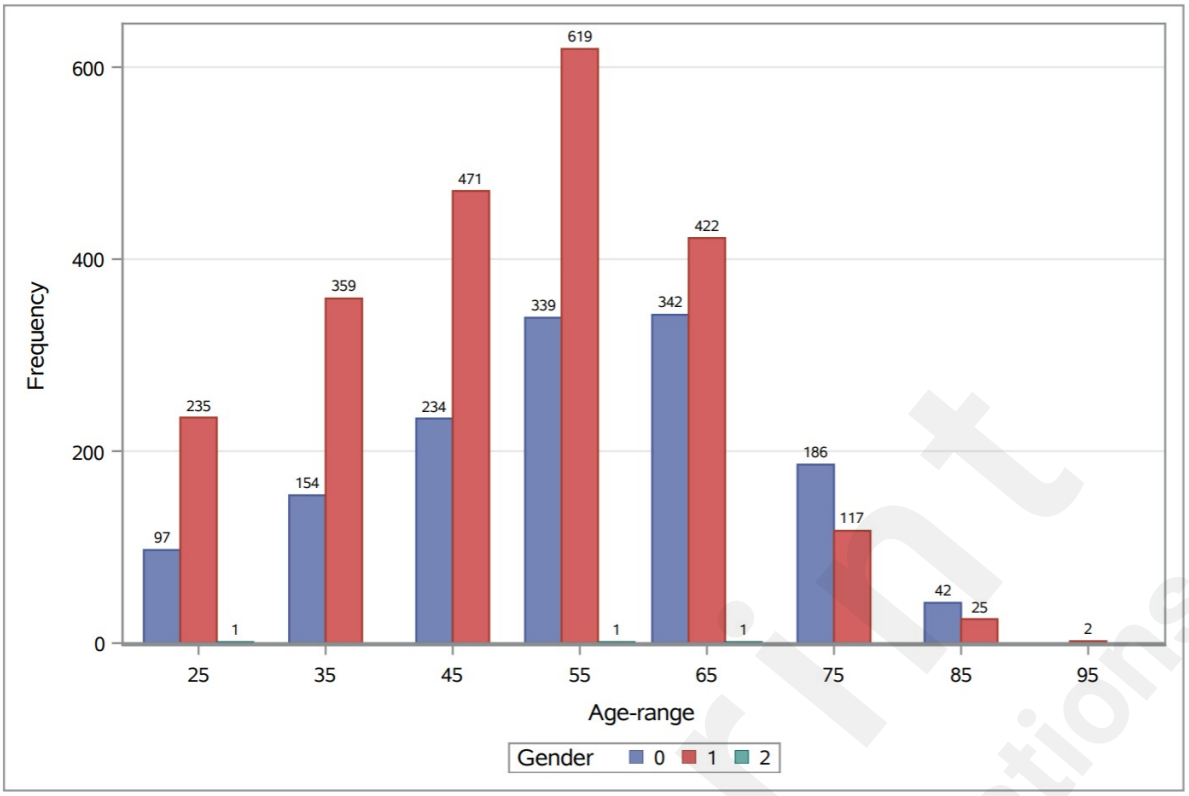

Table 1: Population of the observed district and the mean of the age-ranges in years. A Third Gender was not raised or published.

District of Gifhorn Date: 31.12.2019	Population >=18yrs.			Mean age		
	Total	Male	Female	total	Male	Female
	144156	71811	72345	51.8	50.8	52.8

PCR-Testing for SARS-CoV-2 (PCR)
Out of the 3654 people, 99 were tested at the same time as taking part in the survey. Out of these, 16 people tested positive for SARS-CoV-2.

Medications

We found a significantly lower incidence of typical symptoms for COVID-19 in patients taking statin, antihypertensive, and diuretic medication. DMARDs, metamizole and cortisone were associated with a higher incidence of symptoms. In Table 1 the results of the logistic regression are presented for the specific medication.

Statins: Out of 3654 participants, 358 indicated that they were taking regular medication with statins. The regular intake of statins was significantly associated with a lower incidence of sore throat, dry cough, and headache. Loss of smell or taste, as well as fever, also featured less often in the cohort taking statins. However, this did not reach statistical significance. No association was found between statin medication and the symptoms of shortness of breath and joint or muscle pain. Significant associations were found for women and men in respect to headache, and for women in respect to sore throat despite lowering the statistical power by gender-

segregation (Table3).

Antihypertensives: Out of 3654 participants, 1094 indicated that they were taking regular medication with antihypertensives. These participants on antihypertensives reported a significantly lower incidence of sore throat. Fever and headache were also found less often in this group. However, this association did not reach statistical significance.. The subgroup of ACEIs was found to have a significantly lower incidence of loss of smell or taste.

Furosemide/HCT: 192 participants were taking diuretics, either Furosemide or HCT. Intake of a diuretic was significantly associated with a lower incidence of sore throat.
NSAID, Metamizole: Non steroid anti-inflammatory (NSAID) medication was taken by 212 and Metamizole by 127 participants. Subjects taking NSAID and Metamizole had significantly more typical Covid-19 symptoms.

Table 2: Strength of association between medication and symptoms expressed as Odds-Ratio and the corresponding lower and upper 95% - Wald confidence intervals in brackets. # = not calculable. Statins and antihypertensives highlighted in grey.

Symptom **Medication**	Headache	Fever	Loss of smell-taste	Sore-throat	Shortness of Breath	Joint-Muscle-pain	Dry Cough
	Odds-Ratio Estimates and (lower – upper CI)						
Statins	**0.42 (0.28-0.64)**	0.43 (0.13-1.45)	0.67 (0.29-1.53)	**0.54 (0.35-0.85)**	1.15 (0.71-1.87)	0.87 (0.56-1.34)	**0.61 (0.43 - 0.88)**
NSAID	1.93 (1.38-2.7)	0.4 (0.09-1.67)	0.91 (0.36-2.34)	1.58 (1.08-2.31)	2.36 (1.48-3.75)	2.1 (1.41-3.13)	1.57 (1.1 - 2.23)
Thyroid medication	1.13 (0.89-1.43)	0.63 (0.3-1.32)	0.62 (0.33-1.19)	0.78 (0.59-1.04)	0.84 (0.56-1.26)	1.02 (0.75-1.39)	0.93 (0.72 - 1.2)
Omeprazole/ Pantoprazole	0.95 (0.7-1.3)	1.62 (0.77-3.42)	0.71 (0.33-1.52)	1.15 (0.83-1.61)	0.93 (0.58-1.47)	1.07 (0.74-1.56)	0.81 (0.59 - 1.12)
Metamizole	2.31 (1.5-3.55)	1.47 (0.47-4.56)	2.91 (1.17-7.22)	1.44 (0.87-2.4)	2.62 (1.45-4.73)	2.44 (1.47-4.05)	1.74 (1.1 - 2.74)
Antihypertensives (all)	0.76 (0.55-1.04)	0.48 (0.18-1.26)	1.18 (0.59-2.36)	**0.65 (0.45-0.93)**	1.44 (0.92-2.26)	0.96 (0.65-1.42)	1.22 (0.9 - 1.65)
Furosemide HCT	0.71 (0.44-1.15)	0.58 (0.13-2.64)	0.92 (0.35-2.41)	**0.39 (0.2-0.75)**	0.59 (0.29-1.21)	0.71 (0.4-1.27)	1.02 (0.67 - 1.57)
Cortisone	1.24 (0.83-1.86)	1.47 (0.54-3.98)	0.96 (0.33-2.79)	1.26 (0.81-1.97)	1.83 (1.05-3.18)	1.8 (1.12-2.9)	1.26 (0.82 - 1.92)
DMARDS	0.5 (0.23-1.09)	0.66 (0.08-5.3)	0.82 (0.11-6.33)	1.66 (0.85-3.23)	1.6 (0.69-3.76)	0.54 (0.2-1.45)	1.01 (0.49 - 2.05)
Antihistamines	1.31 (0.94-1.82)	0.73 (0.26-2.07)	0.98 (0.42-2.32)	1.12 (0.77-1.65)	1.22 (0.72-2.05)	0.91 (0.57-1.45)	0.97 (0.67 - 1.41)
Biologics	1.75 (1.18-2.59)	1.32 (0.46-3.79)	0.24 (0.03-1.79)	0.85 (0.51-1.43)	0.57 (0.25-1.28)	0.92 (0.52-1.63)	0.95 (0.59 - 1.52)
Hydroxy-chloroquine	1.8 (0.76-4.25)	1.72 (0.22-13.8)	#	1.66 (0.66-4.16)	0.97 (0.26-3.54)	0.49 (0.11-2.15)	1.44 (0.59 - 3.54)
Subgroup ARBs	0.87 (0.33-2.34)	#	#	0.52 (0.12-2.21)	1.21 (0.35-4.14)	0.9 (0.26-3.05)	1.14 (0.48 - 2.67)
Subgroup ACEis e.g. Ramipril	0.94 (0.65-1.37)	0.93 (0.31-2.83)	**0.38 (0.15-0.93)**	1.16 (0.76-1.75)	0.85 (0.5-1.44)	1.12 (0.72-1.74)	0.93 (0.66 - 1.31)

Subgroup Beta-Blockers	0.95 (0.65-1.37)	1.9 (0.66-5.46)	2.1 (1.01-4.35)	1.24 (0.82-1.87)	0.82 (0.49-1.39)	1.05 (0.68-1.64)	1.14 (0.81 - 1.59)
Subgroup Ca-Channel-blockers e.g. Amlodipine	1.35 (0.88-2.06)	1.14 (0.31-4.16)	1.49 (0.65-3.39)	1.23 (0.75-2)	0.74 (0.38-1.46)	0.66 (0.36-1.19)	1.06 (0.7 - 1.59)

Table 3: Gender segregated strength of association between statins and symptoms expressed as Odds-Ratio and the corresponding lower and upper 95% - Wald confidence intervals in brackets.

Symp-toms **Statins**	Headache	Fever	Loss of smell-taste	Sore-throat	Shortness of Breath	Joint-Muscle-pain	Dry Cough
	Odds-Ratio Estimates and (lower – upper CI)						
Female	**0.3 (0.15 - 0.59)**	0.63 (0.15 - 2.61)	0.85 (0.26 - 2.76)	**0.27 (0.12 - 0.61)**	1.28 (0.63 - 2.57)	0.77 (0.38 - 1.53)	0.84 (0.5 - 1.42)
Male	**0.58 (0.35 - 0.95)**	0.21 (0.03 - 1.58)	0.68 (0.24 - 1.95)	0.73 (0.44 - 1.2)	1.23 (0.67 - 2.25)	0.97 (0.59 - 1.6)	0.65 (0.41 - 1.02)

When making a presumptive diagnosis of COVID-19 infection, either by a positive PCR-test or by using the presence of 4 out of 7 symptoms, we found 142 out of 3654 infections. The statistical analyses revealed a marked inverse association of COVID-19 cases and statins with an OR of 0.29 (0.1 - 0.81). All other medication did not show a significant negative association (Table 4).

Table 4: strength of association between statins and presumed COVID-19 infection by symptoms (minimum 4 out of 7 symptoms positive) expressed as Odds-Ratio and the corresponding lower and upper 95% - Wald confidence intervals in brackets.

Medication	Odds-Ratio Estimates and (lower – upper CI)	Medication	Odds-Ratio Estimates and (lower – upper CI)
Statins	**0,28 (0,1 - 0,78)**	DMARDS	0,9 (0,25 - 3,23)
NSAID (diclophenac. ibuprofen)	1,75 (0,93 - 3,27)	Antihistamines	1,1 (0,58 - 2,08)
Thyroid medication	1,01 (0,64 - 1,62)	Biologics	0,3 (0,07 - 1,24)
Omeprazole/ Pantoprazole	1,1 (0,61 - 2)	Hydrochloroquine	1,33 (0,28 - 6,24)
Metamizole	1,75 (0,77 - 3,97)	Subgroup ARBs_Sartane	1,19 (0,15 - 9,25)
Antihypertensives (all)	0,63 (0,32 - 1,24)	Subgroup ACEis e.g. Ramipril	1,17 (0,55 - 2,47)
Furosemid_HCT	0,24 (0,06 - 1,03)	Subgroup Beta-Blockers	0,9 (0,25 - 3,23)
Cortisone	1,83 (0,91 - 3,66)	Subgroup Ca-Channel-blockers e.g. Amlodipin	1,1 (0,58 - 2,08)

Discussion

Currently the world continues to search for a medication to cure or attenuate COVID-19 infection. It would be desirable, and fortuitous, to identify such a medication already in use for another condition and whose side effect profile and safety data are already known and approved. In the search for such a medication, we combined a symptom surveillance survey with a prospective observational study to identify medications, pre-existing illnesses and vaccination-status with associations to a lower incidence of COVID-19; either proven by PCR testing, hospital admission, professional treatment or typical symptoms.
Fortunately, the incidence of proven SARS-CoV-2-infections was low in the observed area in Lower Saxony. The Robert-Koch-Institute (RKI) recorded 208 PCR-positive tested people and 4 deaths by COVID-19 during the observed time period and area [2]. As a consequence, the prevalence of COVID-19 PCR-tests was low in our participants preventing a meaningful statistical evaluation between medication and test results. Nevertheless, the statistical evaluation of the data demonstrated significant results in respect to typical COVID-19 symptoms and medication intake.

Symptoms
In order of prevalence the following symptoms were found in laboratory confirmed SARS-CoV-2 infected patients admitted to Wuhan hospital: fever, dyspnea, dry cough, myalgia, sputum production, headache and diarrhea [4]. Later on, ageusia and anosmia, as well as a higher incidence of abdominal problems, were also recognized as typical symptoms [7,9]. A current study identifies chills, fever, loss of smell, nausea and vomiting, and shortness of breath, as the top five strongest predictors for COVID-19 infection. Furthermore, they stress that loss of taste and smell should be recognized as cardinal symptoms [10].
The current prospective surveillance survey requests participants record only the positive presence of symptoms (dry cough, sore throat, fever, myalgia or arthralgia, shortness of breath, loss of smell and taste, and headache) if they are new occurrences.
We did not search for gastro-intestinal symptoms such as abdominal cramping or diarrhea.

This was because on initiation of the survey at the beginning of march, gastrointestinal symptoms were considered an uncommon symptom with an incidence of 3 % [4]. The ongoing survey has incorporated these items into the questionnaire.
A Cochrane review found six symptoms in at least one study with a sensitivity of more than 50%: cough, sore throat, fever, myalgia or arthralgia, fatigue, and headache. Fever, myalgia or arthralgia, fatigue, and headache were considered as red flags as their specificity was over 90%, resulting into a positive likelihood ratio of at least 5 for COVID-19 [9].
The major finding of this survey was significant associations between certain medications and either a higher or lower incidence of typical COVID-19 symptoms.

Medication associated with a higher incidence of typical COVID-19 symptoms
We found the medication NSAID or metamizole was significantly associated with all evaluated symptoms except for fever. This seems to be an obvious finding as NSAID and Metamizole are typical medications for treating such symptoms. Cortisone was associated with a significantly higher incidence of “dry cough” and with suspected COVID-19 cases based on symptoms. It could be assumed that patients suffering from COPD regularly take cortisone and present with this symptom more often. Such reasons may explain these statistical results. Nevertheless, these findings are important as a positive indicator to the reliability of the data given by the participants.

Medication with significant lower typical COVID-19 symptoms
The most significant associations were found for hydroxymethyl-glutaryl-coenzyme A reductase inhibitors (statins). These symptoms were dry cough, sore throat, and headache. In addition, statins were associated with a lower incidence of fever, joint or muscle pain and loss of smell or taste. However, these associations did not reach statistical significance. Despite lowering the statistical power by dividing the cohort into female and male, this result was even more obvious for women. When we defined COVID-19 infection as the positive presence of 4 out of the 7 accessed symptoms or by a positive PCR-Test, the result was even more obvious with an OR of 0.28 (0.1 - 0.78).
Furthermore, we found antihypertensives were associated with a significantly lower incidence of “dry cough”. There was also a tendency to a decreased reporting of fever and headache. The statistical analyses of the subgroups ARBs, ACEIs, beta-blockers and calcium-channel-antagonists led to insignificant results except for an association between ACEIs and loss of smell or taste (OR 0.38 (0.15-0.93)). This might be of interest, as loss of smell and taste are recently proposed to be cardinal symptoms for COVID-19 [10]. As the subgroups were very small, the latter results are interpreted with caution.

What is the link between our results and COVID-19?
Statins
In our opinion there are two most likely explanations.
A) Statin therapy may either prevent SARS-CoV-2 infection or lower the symptom burden of a COVD-19 infection. This hypothesis is in line with two current clinical studies. In a retrospective study on 154 nursing home residents with COVID-19 infection, statin therapy was significantly associated with the absence of symptoms [11]. The researchers defined COVID-19 infection by, either a positive PCR test, or by the presence of typical COVID-19 symptoms. However, the exact clinical criteria were not defined. It was argued that none of the diagnostic tools for COVID-19 give a high specificity and sensitivity on their own. They accepted a clinical diagnosis as equivalent to positive PCR testing based on previous studies [12]. Based on this assumption and following the Cochrane review about signs and symptoms of infection with

COVID-19 [9], we defined COVID-19 infection in our group by the positive presence of 4 out of 7 symptoms. The result of the association with statin therapy increased using this definition. In contrast, we did not find associations between the other evaluated medications and symptom defined COVID-19. A second study (Zhag et al) supports the direct influence of statins on COVID-19. They found a significantly lower mortality in COVID-19 hospitalized patients taking concomitant statin medication.
In order to hypothesize that statins reduce the incidence of CoVID-19- symptoms, we have assumed that there was a high number of unknown COVID-19 cases in our participating group at the time of the study. This can only be estimated because of the low rate of PCR-testing available at that time.
On first sight, is looks quite unlikely that statins are able to prevent a SARS-CoV-2 infection. However, a direct protective effect of statins against SARS-CoV-2 infection, is recently proposed by an experimental study by Reiner et. al. using a molecular docking study [13]. From our results so far, it would be premature to assess whether statins have a preventative effect. We hope that our prospective study will shed further light on this potential when more of our participants are tested by PCR.

B) The encountered symptoms are independent of COVID-19. The evaluated symptoms are recognized as typical for COVID-19, but exist in other illnesses such as allergies, non-COVID 19 flu-like virus infections or migraine. Statins might act on those symptoms independently of COVID-19. In this context, it was shown that statins in combination with vitamin D can reduce migraine [14]. Furthermore, the results of previous studies point to the fact that statins are an option for treating the symptoms of influenza [15,16] and pneumonia [17-19]. In summary, it is already accepted that statins have pleiotropic anti-inflammatory and immunomodulatory effects [20] which would explain our findings.
In addition, a combination of A) and B) i.e. an anti-inflammatory effect on both COVID-19 and non-COVID-19 illness, could explain the finding of significant associations between statins and typical COVID-19 symptoms.

Antihypertensives
Currently, there is a widespread discussion about hypertensive medication as a possible treatment option against COVID-19 [11, 21-23]. It is postulated that SARS-CoV-2 enters host cells by binding to the membrane bound form of angiotensin-converting enzyme 2 (ACE2). ACE2 serves as a coreceptor for the virus [22]. Prior to the recognition of COVID-19, angiotensin receptor blockers (ARBs) as well as angiotensin converting enzyme inhibitors (ACEIs) had already been recognized as effective in treating viral pneumonia [18,19]. The tendency for a positive effect on headache, is in line with previous studies demonstrating a positive effect of ACEIs and ARBs on migraine [24,25].

Relevance of the findings

Regardless of whether statins and antihypertensives act on symptoms linked to COVID-19, or whether they act on symptoms independent of COVID-19, we must keep in mind that those symptoms might be masked by this medication. Surveillance recommendations and medical assessments based on typical symptoms may not be reliable in subjects taking statins and antihypertensives. Although not impossible [13], it is very unlikely that statins prevent SARS infection with SARS-CoV-2 infection, as discussed above. If statins do not act to prevent infection, then our results may indicate that stains reduce, or mask, COVID-19 symptoms. In this scenario, people on statin therapy may be more likely to have asymptomatic infection and therefore at greater risk of transmitting the infection unknowingly.

At this point, it should be clearly stated, that our results should not be interpreted as a recommendation to take statins or hypertensive drugs for prevention of COVID-19. We are mindful of the fact that large studies have shown no positive effect of statins in intensive care patients and in sepsis-associated acute respiratory distress syndrome [26,27]. Furthermore, a large study has been discontinued because of lack of benefit and evidence of significant early renal and liver failure while taking rosuvastatin medication [28]. Nevertheless, our data support the hypothesis that statins and antihypertensives may play a role in COVID-19 and emphasizes the potential value of ongoing clinical studies (e.g. NCT04348695, NCT04343001, NCT04351581). In due course as more antibody and PCR tests are performed in this region, we hope to get further insights into the significant associations between the medications discussed and typical COVID-19 symptoms by using our survey to evaluate the follow-up questionnaires.

Limitations of the study

The results are based on a self-selected group who are not necessarily representative of the general population; therefore, bias cannot be ruled out. The possibility of confounding factors is incalculable although bias solely on the grounds of statin medication seems unlikely. The nature of self-assessment of symptoms is purely subjective. However, we found plausible data from the NSAID, metamizole, and cortisone medication groups which indicated that the participants took reporting symptoms seriously. Last but not least, in most cases we lacked laboratory confirmation of COVID-19 infection. We hope that the ongoing-follow-up of this prospective survey will give answers to coherences between medication and PCR proven COVID-19.

Conclusions

The study finds a significant association between statin therapy, and to a lesser extent, antihypertensive therapy and a reduced incidence of typical COVID-19 symptoms in a self-selected group of people in Lower saxony, Germany.
We propose that statin therapy masks the symptoms in people infected with SARS-CoV-2. This is especially the case for women and for symptoms of dry cough, headache, and sore throat. This result of this study should be incorporated into all ‘symptoms-based’ surveillance and decision-making protocols in respect to COVID-19. Furthermore, people taking statin therapy may be more likely to have an asymptomatic COVID-19 infection, in which case they are at an increased risk of transmitting it unknowingly.
The exact link between statins and the finding of reduced symptoms in the study population, with a possible therapeutic or preventive effect of statins on COVID-19, remains unclear. Our ongoing surveillance with data acquisition of symptoms, medication, and testing for COVID-19 will hopefully give more insights into this question in the near future.

Abbreviations

ARB: angiotensin receptor blocker
ACEI: angiotensin converting enzyme inhibitor
CI: confidence interval
COVID-19: coronavirus disease 2019
HCT: Hydrochlorothiazide
NSAID: Non-steroidal anti-inflammatory drug
DMARD: Disease modifying anti rheumatic Drug
RKI: Robert-Koch-Institute, Germany

RT-PCR: reverse transcription polymerase chain reaction:
WHO: World Health Organization
SARS: severe acute respiratory syndrome
“Statins”: Hydroxymethyl-glutaryl-coenzyme A reductase inhibitors
Yrs.: Years

Conflicts of Interest

None declared

REFERENCES

1. WHO coronavirus disease (COVID-19) dashboard. Geneva: World Health Organization, 2020. Accessed July 19, 2020. https://covid19.who.int

2. Robert Koch-Institut: Erfassung der SARS-CoV-2-Testzahlen in Deutschland (Update vom 15.4.2020). Epid Bull 2020;16:10 | DOI. Epid Bull. 2020;(16):10. doi:10.25646/6756.3

3. Böhmer MM, Buchholz U, Corman VM, et al. Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series. Lancet Infect Dis. Published online May 15, 2020. doi:10.1016/S1473-3099(20)30314-5

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

5. Covián C, Retamal-Díaz A, Bueno SM, Kalergis AM. Could BCG Vaccination Induce Protective Trained Immunity for SARS-CoV-2? Front Immunol. 2020;11:970. doi:10.3389/fimmu.2020.00970

6. Sharma A, Kumar Sharma S, Shi Y, et al. BCG vaccination policy and preventive chloroquine usage: do they have an impact on COVID-19 pandemic? Cell Death Dis. 2020;11(7):516. doi:10.1038/s41419-020-2720-9

7. Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020;26(7):1037-1040. doi:10.1038/s41591-020-0916-2

8. Echeverría P, Mas Bergas MA, Puig J, et al. COVIDApp as an Innovative Strategy for the Management and Follow-Up of COVID-19 Cases in Long-Term Care Facilities in Catalonia: Implementation Study. JMIR Public Health Surveill. 2020;6(3):e21163. doi:10.2196/21163

9. Struyf T, Deeks JJ, Dinnes J, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database Syst Rev. 2020;7:CD013665. doi:10.1002/14651858.CD013665

10. Zens M, Brammertz A, Herpich J, Südkamp N, Hinterseer M. App-based tracking of self-reported COVID-19 symptoms. J Med Internet Res. Published online July 26, 2020.

doi:10.2196/21956

11. De Spiegeleer A, Bronselaer A, Teo JT, et al. The Effects of ARBs, ACEis, and Statins on Clinical Outcomes of COVID-19 Infection Among Nursing Home Residents. J Am Med Dir Assoc. 2020;21(7):909-914.e2. doi:10.1016/j.jamda.2020.06.018

12. Lovato A, de Filippis C. Clinical Presentation of COVID-19: A Systematic Review Focusing on Upper Airway Symptoms. Ear Nose Throat J. Published online April 13, 2020:145561320920762. doi:10.1177/0145561320920762

13. Reiner Ž, Hatamipour M, Banach M, et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. Arch Med Sci. 2020;16(3):490-496. doi:10.5114/aoms.2020.94655

14. Buettner C, Nir R-R, Bertisch SM, et al. Simvastatin and vitamin D for migraine prevention: A randomized, controlled trial. Ann Neurol. 2015;78(6):970-981. doi:10.1002/ana.24534

15. Fedson DS. Clinician-initiated research on treating the host response to pandemic influenza. Hum Vaccin Immunother. 2018;14(3):790-795. doi:10.1080/21645515.2017.1378292

16. Fedson DS. Treating influenza with statins and other immunomodulatory agents. Antiviral Res. 2013;99(3):417-435. doi:10.1016/j.antiviral.2013.06.018

17. Sapey E, Patel JM, Greenwood H, et al. Simvastatin Improves Neutrophil Function and Clinical Outcomes in Pneumonia. A Pilot Randomized Controlled Clinical Trial. Am J Respir Crit Care Med. 2019;200(10):1282-1293. doi:10.1164/rccm.201812-2328OC

18. Mortensen EM, Nakashima B, Cornell J, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. Clin Infect Dis. 2012;55(11):1466-1473. doi:10.1093/cid/cis733

19. Henry C, Zaizafoun M, Stock E, Ghamande S, Arroliga AC, White HD. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. Proc (Bayl Univ Med Cent). 2018;31(4):419-423. doi:10.1080/08998280.2018.1499293

20. Lee KCH, Sewa DW, Phua GC. Potential role of statins in COVID-19. Int J Infect Dis. 2020;96:615-617. doi:10.1016/j.ijid.2020.05.115

21. Sanchis-Gomar F, Perez-Quilis C, Favaloro EJ, Lippi G. Statins and other drugs: Facing COVID-19 as a vascular disease. Pharmacol Res. 2020;159:105033. doi:10.1016/j.phrs.2020.105033

22. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol. 2020;318(5):H1084-H1090. doi:10.1152/ajpheart.00217.2020

23. Wang Q, Zhang Y, Wu L, et al. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. Cell. 2020;181(4):894-904.e9. doi:10.1016/j.cell.2020.03.045

24. Nandha R, Singh H. Renin angiotensin system: A novel target for migraine prophylaxis. Indian J Pharmacol. 2012;44(2):157-160. doi:10.4103/0253-7613.93840

25. Rau JC, Dodick DW. Other Preventive Anti-Migraine Treatments: ACE Inhibitors, ARBs, Calcium Channel Blockers, Serotonin Antagonists, and NMDA Receptor Antagonists. Curr Treat Options Neurol. 2019;21(4):17. doi:10.1007/s11940-019-0559-0

26. Kruger P, Bailey M, Bellomo R, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med. 2013;187(7):743-750. doi:10.1164/rccm.201209-1718OC

27. Pertzov B, Eliakim-Raz N, Atamna H, Trestioreanu AZ, Yahav D, Leibovici L. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults - A systematic review and meta-analysis. Clin Microbiol Infect. 2019;25(3):280-289. doi:10.1016/j.cmi.2018.11.003

28. Truwit JD, Bernard GR, Steingrub J, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med. 2014;370(23):2191-2200. doi:10.1056/NEJMoa1401520

Supplementary Files

Figures