NIPH
Norwegian Institute of Public Health

REPORT

2023

RAPID REVIEW

Post COVID-19 condition after Omicron

Title	Post COVID-19 condition after Omicron
Institution	Norwegian Institute of Public Health/ Folkehelseinstituttet
Responsible	Camilla Stoltenberg, Director-General
Authors	Himmels JPW, *senior advisor*, *Norwegian Institute of Public Health*
	Hilde Marie Lund, *doctor, Norwegian Institute of Public Health*
	Brurberg KG, *head of Department*; *Norwegian Institute of Public Health*
ISBN	978-82-8406-388-1
Publication type	Rapid review
Number of pages	15 (18 appendices included)
Commissioned by	Norwegian Institute of Public Health/ Folkehelseinstituttet
Citation	Himmels JPW, Lund HM, Brurberg KG Post COVID-19 condition after Omicron [Senfølger etter covid-19 som følge av omikronsmitte: hurtigoversikt 2023] Oslo: Norwegian Institute of Public Health, 2023.

English Summary

Background

Most people will experience COVID-19 as a mild and transient disease, although some may experience a prolonged period with symptoms. Long-term and nonspecific symptoms have previously been reported following other viral infections, and after bacterial and parasitic infections. It is also known that people who are admitted to the intensive care unit due to severe lung failure caused by other diseases than COVID-19, can report long-term functional impairments such as impaired cognitive function, mental health problems and reduced lung function after discharge. As of early 2023, most of the Norwegian population is vaccinated and has undergone an infection with the Omicron variant. We are not aware of research relevant on this population group compared to non-COVID-19 controls, hence there is a need to review primary research systematically.

Objectives

We aimed to summarise research on the proportion of patients who report long-term symptoms at least 6 months after Omicron infection, which long-term symptoms occur after COVID-19 due to the Omicron variant, how long the symptoms persist and which patient groups that have the greatest risk of experiencing long-term symptoms.

Methods

We have previously published a rapid review about Post COVID-19 condition that was last updated in December 2022. The review published in December 2022 included data on all previous SARS-CoV-2 variants, whereas the current review is limited to post COVID-19 condition following infections caused by Omicron. This report supplements the December 2022 report, in which we limited our search to probable Omicron cases. We included controlled studies with more than 300 mainly laboratory test positive COVID-19 cases with a follow-up time of six months or longer. We excluded studies mainly reporting on laboratory or radiological findings, uncontrolled studies, and controlled studies that had not been peer-reviewed.

The findings are based on systematic searches in MEDLINE and WHO Global research on coronavirus disease (COVID-19) database on April 14th, 2023. Two researchers screened the search results with machine learning support.

Results

We screened 6918 studies. No studies matching our inclusion criteria were identified.

Discussion

There is a lack of controlled studies examining the long-term effects of the Omicron variant compared to non-COVID-19 controls including vaccinated patients who experienced mild or moderate disease. The latter population is especially relevant to the Norwegian setting. While there are initial studies with short follow-up indicating a lower prevalence of long-term symptoms after Omicron infections, it is crucial to conduct more controlled studies to obtain reliable and comprehensive data.

Generalizing early findings from different populations to the broader society can be misleading and may not accurately reflect the specific situation in Norway. While the urgency of the pandemic has understandably driven researchers to publish their findings quickly, it is essential to prioritize thoroughness and quality in the research process. We see a need to conduct a new search for relevant research within a year of our search, to provide an up to date and reliable overview of evidence.

Conclusion

There is a lack of controlled studies that have investigated the long-term symptoms following an Omicron infection compared to non-COVID-19 controls. Preliminary evidence suggests that the health impacts after an Omicron infection differ in comparison to other SARS-CoV-2 variants. The earliest studies suggest that there may be a lower likelihood of long-term symptoms associated with Omicron. Assumptions derived from studies conducted during the early stages of the pandemic are less relevant to the current context. This is of particularly relevance in Norway, where most of the population was vaccinated prior to infection to the clinically milder Omicron variant. There is a need for controlled studies to be conducted on the late effects that may result from an Omicron infection to guide public policy decisions.

Norsk sammendrag

Bakgrunn

For de fleste gir covid-19 mild og forbigående sykdom, men noen opplever at det tar tid å bli kvitt alle symptomer. Slike langvarige og uspesifikke symptomer er også tidligere rapportert i etterkant av andre infeksjoner forårsaket av virus, bakterier og parasitter. Det er også kjent at personer som har vært innlagt i intensivavdeling grunnet alvorlig lungesvikt forårsaket av andre sykdommer enn covid-19 kan oppleve langvarige funksjonsnedsettelser som nedsatt kognitiv funksjon og redusert lungefunksjon etter utskrivelse. Brorparten av den voksne befolkningen i Norge er nå vaksinert, og de fleste har også gjennomgått infeksjon med omikron. Vi kjenner ikke til kontrollerte studier som har undersøkt senfølger etter infeksjon med omikron sammenlignet med kontroller uten covid-19, og det er derfor behov for en systematisk gjennomgang av primærstudier.

Problemstilling

Vi ønsket å oppsummere forskning som har undersøkt hvor mange pasienter som rapporterer langvarige symptomer etter covid-19 forårsaket av omikron, hvilke senfølger som rapporteres, hvor lenge symptomene vedvarer og hvilke pasientgrupper som har størst risiko for å oppleve senfølger.

Metoder

Folkehelseinstituttet har tidligere publisert en hurtigoversikt om senfølger etter covid-19 som sist ble oppdatert i desember 2022. Oversikten fra desember 2022 inkluderer data på alle tidligere varianter av SARS-CoV-2, men denne oversikten er avgrenset til senfølger som oppstår etter smitte med omikron-varianten. I denne versjonen har vi avgrenset søket til studier som omfatter sannsynlige omikron-tilfeller. Vi ønsket å inkludere kontrollerte studier med mer enn 300 hovedsakelig testpositive covid-19-tilfeller med en oppfølgingstid på seks måneder eller lenger. Vi ekskluderte studier som primært rapporterte laboratorieresultater eller radiologiske funn, studier uten kontrollgrupper og studier som ikke var fagfellevurderte.

Vi gjennomførte systematiske litteratursøk i MEDLINE og WHO Global research on coronavrius disease (COVID-19) database 14. april 2023. To forskere gjennomgikk søkeresultatene med støtte fra maskinlæring.

Resultater

Vi screenet 6918 studier, men identifiserte ingen studier som oppfylte våre inklusjonskriterier.

Diskusjon

Det finnes få kontrollerte studier som undersøker senfølger etter infeksjon med omikron sammenlignet med kontroller uten covid-19, noe som også gjelder studier som undersøker senfølger blant vaksinerte som gjennomgår mildt til moderat akutt forløp. Disse gruppene er særlig relevante for den norske befolkningen. Det finnes foreløpig enkelte studier med kort oppfølging som antyder lavere forekomst av senfølger blant omikron-pasienter, men det er behov for flere kontrollerte studier for å skaffe pålitelige data og et bedre kunnskapsgrunnlag.

Å generalisere funn fra tidlige studier i ulike populasjoner til den generelle befolkningen kan være misvisende og gjenspeiler ikke nødvendigvis situasjonen slik den er i Norge. Selv om det under pandemien har vært behov for å publisere ny kunnskap svært raskt, er det nå nødvendig å prioritere grundighet og kvalitet i forskningsprosessen. Etter vårt syn vil det være nødvendig å gjennomføre et nytt litteratursøk innen et år fra vårt søk for å skaffe en oppdatert og pålitelig oversikt over gjeldende kunnskap.

Konklusjon

Det er mangel på kontrollerte studier som har undersøkt senfølger etter infeksjon med omikron sammenlignet med kontroller uten covid-19. Foreløpige funn antyder at forekomsten av senfølger etter omikron er lavere sammenlignet med andre SARS-CoV-2-varianter. Funn fra studier utført tidlig i pandemien kan derfor ha begrenset relevans for dagens situasjon. Dette gjelder særlig i Norge, der de fleste i befolkningen ble vaksinert før de ble smittet av den klinisk mildere omikron-varianten. Det er behov for kontrollerte studier som undersøker senfølger etter omikron for å støtte offentlig beslutningstaking.

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Problem statement

COVID-19 has been associated with long-term symptoms. Aiming to offer customised treatment, policy makers, health care professionals and patients need access to up-to-date evidence about long-term symptoms after COVID-19. Since the Omicron variant has replaced earlier variants, in the 5th version of this rapid review, we searched evidence aiming to explore:

1. Which proportion of Omicron patients experience long-term symptoms at least six months after COVID-19?
2. Which symptoms after Omicron are seen in post COVID-19 condition?
3. Which factors are associated with long-term symptoms of COVID-19 after Omicron?
4. How does post COVID-19 condition after Omicron differ from long-term effects of other respiratory tract infections?

The post COVID-19 condition team at the Norwegian Institute of Public Health (NIPH) has commissioned this rapid review as a supplementary follow-up to a rapid review published 19th December 2022 (1).

Methods

Literature search

We applied an open search strategy to identify all relevant studies on the prevalence of long-term COVID-19 symptoms, demographic and medical risk factors associated with symptoms on follow-up, and studies analysing the impact of long-term symptoms of COVID-19. We defined the inclusion criteria prior to the search. We included studies of participants with confirmed COVID-19, that reported on symptoms, quality of life, and predicting factors for long-term symptoms. One researcher (JH) conducted the search on April 14th, 2023, in the MEDLINE database for studies published in the period 01.07.2022 -13.04.2023. We expanded this search with a search in the WHO Global research on coronavirus disease (COVID-19) database on April 14th, 2023 (limited to 2022-23; five databases: EMBASE, EuropePMC, Scopus, ProQuest Central, Web of Science, and English language)(Appendix 1).

Inclusion criteria:

Population:	More than 300 COVID-19 positive participants followed up with non-COVID-19 controls, infected with identified omicron variant or after 1.01.22 (or studies reporting on the omicron subgroup specifically)
Outcome:	Any long-term symptoms, consequences associated with COVID-19 (excluding studies only/mainly reporting on laboratory or radiological findings)
Follow-up:	Included participants followed up for median/mean six months or longer. Studies reporting cumulative/aggregated follow-up data combined for the acute phase (first 3 months) and beyond were excluded, unless compared with another acute illness.
Study types:	Cohort studies (prospective and retrospective), case-controls, registry-based studies, cross-sectional surveys
Excl. criteria:	Non-peer-reviewed studies, abstracts, letters, studies limited to participants with one main underlying disease

Review process

Two researchers (JH, HL) performed title and abstract screening supported by machine learning. Two researchers (JH, HL) planned to review studies in full text, select studies for inclusion, extract, and summarise data/results from included studies in tables. A senior researcher in the field provided feedback for the study selection process and methodological approach (KGB).

Quality assessment

It was planned that two reviewers would use the RoB SPEO tool developed by the World Health Organisation and the International Labour Organisation to assess the risk of bias of included studies (2). We would have resolved any uncertainty regarding the risk of bias of a study through discussion among review authors. We did not plan to assess the certainty of the available evidence.

Data extraction

We planned to extract information on study country, participants, follow-up period, symptom prevalence and statistics (e.g., odds ratio, rate ratio, hazard ratio). We planned to describe studies with participants mainly below 18 years of age separately.

Data analysis

We planned to export data tables of extracted endpoints to Microsoft Excel and PowerPoint for data analysis and visualisation. Visualisations were to be based on available datapoints.

Peer review

Since no studies were identified we did not consider peer review necessary.

Results

Description of studies

Results of the literature search

We identified zero unique references matching our inclusion criteria through the systematic literature searches. JH and HL screened all potentially relevant titles and abstracts in EPPI reviewer (3). We screened 3214 references with priority screening. We used studies included in our previous reviews as a basis to train a machine learning model (Appendix 2). No unique studies matched our inclusion criteria.

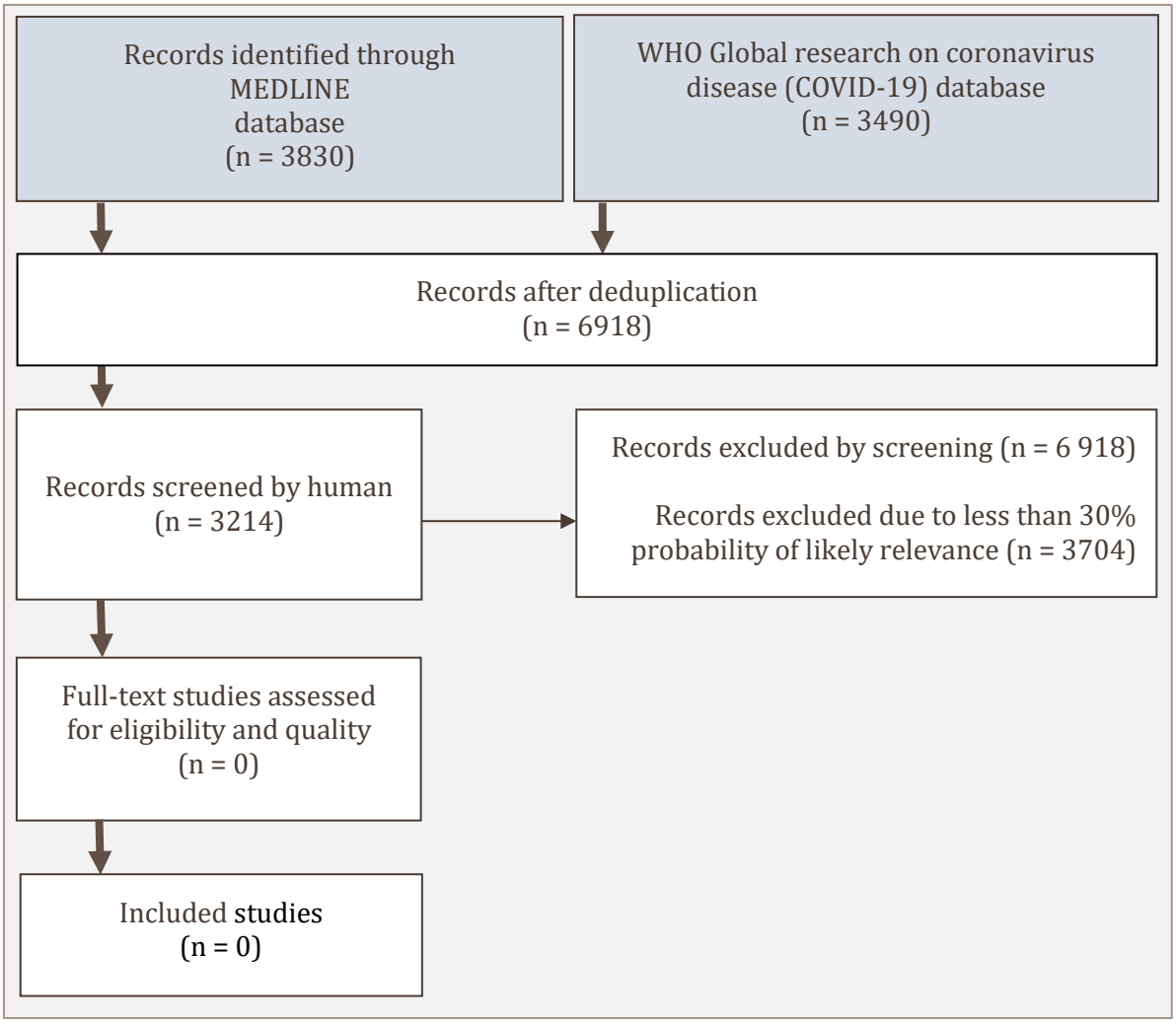

Figure 1. Flow diagram of search strategy and study inclusion

Discussion

We were not able to identify any studies following up participants with COVID-19 Omicron variant and non-COVID-19 controls for six months or longer. Our previous review on post-COVID-19 condition published in December 2022 included 14 studies, none of which matched the inclusion criteria for Omicron infected patients. This follow-up report supplements the December 2022 report. An anticipated lesser number of controlled studies on Omicron led us to reduce the number of participants from 500 to 300 without impacting our findings.

Based on our iterative updates, our current findings suggest that the publication speed is slower than expected. Studies that were anticipated to provide variant-specific analysis compared with non-COVID-19 controls have not yet been published. As our fundamental research questions remain unchanged, it is reasonable to expect that the majority of all COVID-19 patients, those infected by Omicron, will be analysed by researchers in an equivalent manner or more thoroughly to those of earlier variants. Our screening of titles and abstracts has shown that the first controlled studies are now being published, indicating that there will soon be studies with sufficient follow-up relevant to the Norwegian population. These early studies on Omicron patients with short follow-up suggest a lower prevalence of long-term symptoms after infection with Omicron compared to other SARS-CoV-2 variants (4, 5, 6, 7, 8). In absence of a systematic search for short follow-up studies we have not come across studies indicating higher prevalence of long-term symptoms or increased severity of long-term symptoms after the acute phase of infection by Omicron.

This systematic review highlights the limited evidence on the population that is most relevant to the Norwegian setting, which is vaccinated individuals experiencing mainly mild or moderate disease following Omicron infection. It is important to exercise caution when generalising early findings from different populations to the overall society. The severity of infection is a risk factor for a reduced quality of life, and ICU patients are the hardest hit. Vaccination has been shown to contribute to milder infections and fewer and shorter symptoms during the post-acute COVID-19 period (9, 10). Given that Omicron infections are generally milder, and that most people in Norway have been vaccinated, earlier findings may be less relevant to the Norwegian population. However, it is crucial to identify reliable data for this variant and not rely on outdated research that was produced under the pressure of a rapidly changing pathogen. The emergence of Omicron marks a new phase of variant stability. The lack of identified studies in this review may suggest a shift away from the rapid publication speed seen in the early pandemic. Possibly pandemic-related research is transitioning to more standard publication timelines, this may contribute to higher quality studies with fewer biases.

We are aware of one recently published systematic review with less stringent inclusion criteria looking at different SARS-CoV-2 Variants of Concern. The authors found a lower prevalence of long-term symptoms after COVID-19 in individuals infected with the Omicron variant compared to earlier variants. However, their open inclusion criteria led the authors to conclude that

heterogeneity and the short follow-up of included studies limits their certainty in the findings (8).

There is an urgent need for controlled studies on the long-term effects of the Omicron variant. Although our knowledge has rapidly grown, early findings are no longer representative of the current challenges the healthcare system faces. We need up to date evidence relevant to the local Norwegian setting. It is also important to investigate how the long-term effects of Omicron vary across diverse population subgroups. Investigating the long-term effects of Omicron is critical for developing comprehensive public health strategies.

Conclusion

There is a lack of controlled studies that have investigated the long-term symptoms following an Omicron infection compared to non-COVID-19 controls. Preliminary evidence suggests that the health impacts after an Omicron infection differ in comparison to other SARS-CoV-2 variants. The earliest studies suggest that there may be a lower likelihood of long-term symptoms associated with Omicron. Assumptions derived from studies conducted during the early stages of the pandemic are less relevant to the current context. This is of particularly relevance in Norway, where most of the population was vaccinated prior to infection to the clinically milder Omicron variant. There is a need for controlled studies to be conducted on the late effects that may result from an Omicron infection to guide public policy decisions.

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Appendix

Appendix 1; Search strategy

Ovid MEDLINE(R) ALL

#	Query	22.01.21	17.06.21	29.10.21	19.09.22	14.04.23
1	chronic covid*.ti,ab,kf.	8	9	33	63	81
2	long covid*.ti,ab,kf.	53	100	545	1797	2952
3	persistent covid*.ti,ab,kf.	10	16	43	132	179
4	(Post acute covid* or postacute covid*).ti,ab,kf.	20	28	141	390	577
5	(Post covid* adj3 (illness* or syndrome* or symptom* or condition*)).ti,ab,kf.	38	59	301	939	1532
6	(Prolonged adj3 covid*).ti,ab,kf.	56	54	181	323	428
7	or/1-6	178	239	1059	3067	4777
8	(chronic adj3 (complication* or infect* or symptom* or syndrome*)).ti,ab,kf.	87977	77846	92094	96840	100010
9	(Long-haul* OR longhaul*).ti,ab,kf.	873	637	1009	1173	1279
10	((long-term or longterm) adj3 (complication* or consequence* or outcome*)).ti,ab,kf.	107129	93199	114984	124216	129942
11	(Persistent adj3 (infecti* or symptom* or syndrome*)).ti,ab,kf.	25675	22945	27044	28885	30113
12	(Prolonged adj3 recovery).ti,ab,kf.	2504	2213	2610	2763	2839
13	sequelae*.ti,ab,kf.	65210	59058	68354	72288	74937
14	or/8-13	282589	249861	298750	318041	330467
15	exp Coronavirus/	45480	77043	102548	150500	165418
16	exp Coronavirus Infections/	49711	94037	125455	198109	230548
17	(coronavirus* or corona virus* or ~~OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or~~ covid* or sars-cov* or sarscov* or Sars-coronavirus* or omicron* or omikron* or Severe Acute Respiratory Syndrome Coronavirus*).mp.	111302	99784	208786	312119	370300
18	(2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.	96949	87824	193062	29572	350885
19	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	39990	4198	5549	8708	1848
20	or/15-19	117249	105657	214812	318301	376013

21	~~20191201:20301231.(dt).~~ ~~/20210122:20301231.(dt)/20210617:20301231.(dt)./~~ ~~20211029:20301231.(dt)/~~ **~~20220701:20301231.(dt)~~**	97953	19473	46125	105024	82579
22	14 and 20					7219
23	7 or 22					10273
24	23 and 21	1105	533	1823	4757	3830

*Alterations marked in red

Search: 2021-09-19: *WHO COVID-19 Global literature on coronavirus disease:*

TW:(long-covid OR "long covid" OR long-haul* OR "long haul" OR "long hauler" OR "long-haulers" OR "lingering complications" OR "long term complications" OR "longterm complications" OR "long-term complications" OR "persistent complications" OR "prolonged complications" OR "sustained complications" OR "lingering effects" OR "long term effects" OR "longterm effects" OR "long-term effects" OR "persistent effects" OR "prolonged effects" OR "sustained effects" OR "lingering symptoms" OR "long term symptoms" OR "longterm symptoms" OR "long-term symptoms" OR "persistent symptoms" OR "prolonged symptoms" OR "sustained symptoms" OR "post-covid syndrome" OR "post covid syndrome" OR survivors OR survivorship OR "post-covid syndrome" OR "post covid syndrome" OR "post covid condition" OR survivors OR survivorship OR omicron OR omikron)

*Alterations since last search marked in red

Results:
22.01.21: 1 291 (until 22.01.21)
17.06.21: 1 304 (for all 2021)
29.10.21: 1 502 (for 17.06-29.10)
19.09.22: 10 592 (2021-22; EMBASE, EuropePMC, Scopus, ProQuest Central, Web of Science, language EN)
14.04.23: 3.490 (2022-23; EMBASE, EuropePMC, Scopus, ProQuest Central, Web of Science; language: EN, Topics: variants & Long Covid)

Appendix 2; Methodology screening

We identified 6918 studies, 3214 studies were screened and excluded by two researchers, 3704 studies were excluded based on less than 30% likelihood of relevance based on a machine learning model.

We initiated screening through EPPI reviewers Priority Screening with single screening by two researchers. We chose to label studies matching solely the **categorical** (topic) criteria as "*includes"*, based on the assumption that **numerical** (dates, participants number, etc.) criteria can appear arbitrary to a machine learning model, and hence undermine the ability of a machine learning model to identify most relevant studies based on similarity. At three intervals we reviewed "*includes*" to finetune the selection of studies used to identify further relevant studies. Upon our last finetuning of "*includes*" it became apparent that none of the categorically relevant studies also satisfied the numerical inclusion criteria. To confirm that we identified all categorical relevant studies we conducted a keyword search for "Omicron", screening 1063 studies with the keyword in title or abstract: no studies matching both categorical and numerical criteria were identified (see figure 2).

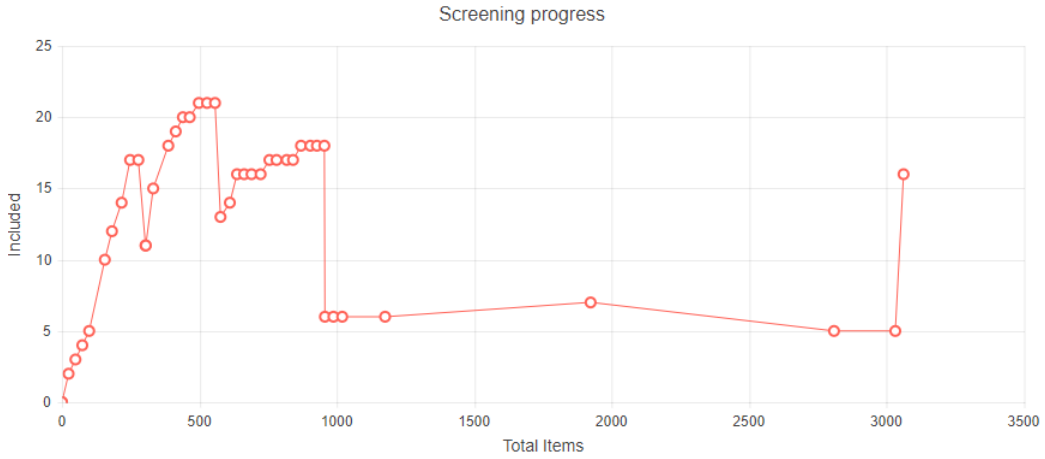

Figure 2. Priority screening EPPI reviewer, 3 drops for each finetuning, and an increase of 10 studies following the building of a machine learning model

After screening a total of 3214 studies we build a machine learning model, to differentiate between categorically relevant studies and already excluded studies. Six "*includes*" from the priority screening plus 10 studies included in our previous report were considered as categorically relevant. We applied the model to the unscreened studies and excluded all studies with less than 30% probability of relevance. Figure 3 depicts the distribution of studies by their likelihood for relevance.

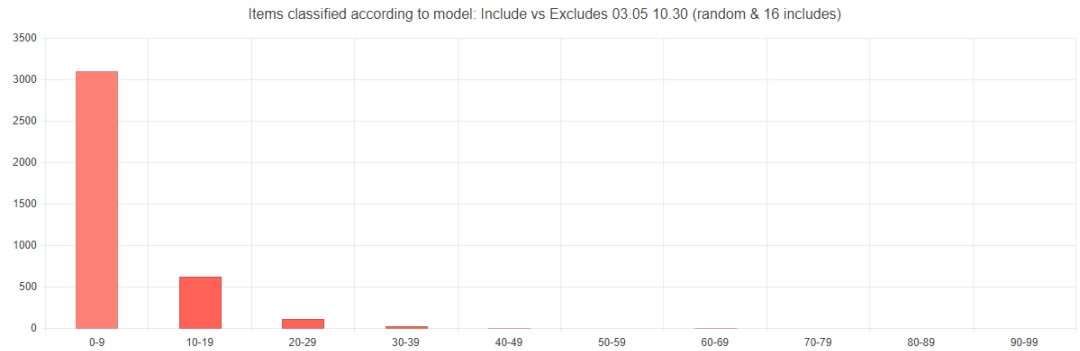

Figure 3. Distribution of non-screened studies based on a machine learning model

Published by the Norwegian Institute of Public Health
July 2023
P.O.B 4404 Nydalen
NO-0403 Oslo
Telefon: + 47-21 07 70 00
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