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Chronic disease patients have fewer social contacts: A pilot survey with implications for transmission dynamics

J. Vanderlocht [a], S. Møgelmose [a], K. Van Kerckhove [a], P. Beutels [b], N. Hens [a, b, *]

[a] Interuniversity Institute of Biostatistics and Statistical Bioinformatics, Data Science Institute, Hasselt University, Hasselt, Belgium
[b] Centre for Health Economic Research and Modelling Infectious Diseases, University of Antwerp, Antwerp, Belgium

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ABSTRACT

Non-communicable diseases (NCD) are the most important cause of death in the world. The socio-economic costs associated with NCDs makes it imperative to prevent and control them in the 21st century. The severe toll that the COVID-19 pandemic has taken worldwide is an unfortunate illustration of our limited insight into the infectious risk for the global population. Co-incidence between NCD and infection offers an underexplored opportunity to design preventive policies. In a pilot survey, we observed that the NCD population displays a substantial reduction in their social contacting behavior as compared to the general population. This indicates that existing mathematical models based on contact surveys in the general population are not applicable to the NCD population and that the risk of acquiring an infection following a contact is probably underestimated. Our demonstration of reduced social mixing in several chronic conditions, raises the question to what extent the social mixing is influenced by the burden of disease. We advocate the design of disease-specific contact surveys to address how the burden of disease associates with social contact behavior and the risk of infection. The SARS-CoV-2 pandemic offers an unprecedented opportunity to gain insight into the importance of infection in the NCD population and to find ways to improve healthcare procedures.

Non-communicable diseases (NCDs) are the most important cause of death in every region of the world and account for more than 70% of overall health care expenditure in the developed world (Lopez et al., 2006). The preponderance of NCDs is increasing as a consequence of advancing epidemiological and demographic transition in low- and middle-income countries, with economic development and associated changes to lifestyle (Stuckler, 2008). Although currently 97% of the healthcare budget in the western world is invested in the treatment of NCDs (Suhrcke et al., 2006), there is consensus that the search for preventive measures is more effective from a global health and health-economic perspective. In particular, the co-incidence between NCD and infection offers an underexplored opportunity to design policies aimed at reducing the occurrence, spread or burden of infection. As well as being intended to translate into a survival benefit, such policies also promise to reduce health care expenditure as NCDs show an increased burden of infection (e.g. higher hospitalization rates for influenza and

* Corresponding author. Centre for Health Economic Research and Modelling Infectious Diseases, University of Antwerp Universiteitsplein 1, 2610, Wilrijk, Belgium.

E-mail address: niel.hens@uantwerpen.be (N. Hens).

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SARS-CoV-2 disease). Furthermore, for specific diseases (e.g. chronic obstructive pulmonary disease; COPD) infection is the driver of disease progression and lung function decline (Wackerhausen & Hansen, 2012), thus, infection-preventative policies modulate progression and thereby the natural disease course.

To date there is limited insight in the NCD population with respect to the height of their susceptibility to infection, their contribution to the spread of an epidemic and the interplay between infection and their underlying disease. The recent SARS-CoV-2 pandemic painfully illustrates the relevance of such knowledge (Bellizzi et al., 2021). In the early days of the SARS-CoV-2 pandemic, it became apparent that NCD patients are overrepresented among hospitalized and deceased individuals (Chen et al., 2020; Grasselli et al., 2020; Guan et al., 2020; Yang et al., 2020a, 2020b). NCD patients (in whom hypertension and diabetes were the most prevalent) composed ≥25% of hospitalized patients, and a wealth of studies has demonstrated the increased risk of adverse outcome in patients suffering from hypertension, diabetes, (COPD), cardiovascular and cerebrovascular disease (Nikoloski et al., 2021). As well as the adverse outcome after SARS-CoV-2, the standard care for NCD patients was disrupted in more than 75% of countries during the pandemic. Furthermore, the sequelae of COVID can aggravate the course an NCD and COVID-related lockdowns contributed to the occurrence of NCD by interfering with the occurrence of obesity, quality of nutrition, alcohol intake and reduced physical activities during lockdowns (COVID-19, 2020).

One of the most important tools to predict the course of an epidemic or pandemic and to design non-pharmaceutical mitigation strategies makes use of mathematical models about how people interact and which of these interactions are potential contact events. A contact event, in this context, is defined as an event involving two individuals such that infection would have been transmitted had the contacting individual been infectious and had the contacted individual been susceptible. A good proxy measure for contact events can be deducted from contact surveys. At present, it remains unclear whether mathematical models based on contact surveys in the general population are applicable to the NCD population (Hoang et al., 2021). Previously, we and others have reported on the relevance of specifically designed contact surveys that address the reprogramming of social mixing upon influenza-like illness (ILI). In that survey, we reported that not only the number but also the age-distribution of contacts altered in symptomatic individuals and coupling of these data with mathematical models in which the contact behavior changes from asymptomatic to symptomatic demonstrated a significant impact on the basic reproduction number (R_0) and the age distribution of cases in the population (Van Kerckhove et al., 2013). Such models can also be applied to estimate the relative contribution of symptomatic vs asymptomatic individuals based on the incidence of new cases in an early epidemic and to estimate the difference in infectiousness between symptomatic and asymptomatic individuals. For example, using this methodology we inferred that, symptomatic individuals generated 2/3 of the newly infected individuals in the influenza A/H1N1pdm pandemic in England and Wales and were therefore 3–12 times as infectious compared with asymptomatic persons (Van Kerckhove et al., 2013). The concept that altered contact patterns upon ILI impact the spread of an epidemic is intuitive, and it stands to reason that it extends to other illnesses.

Here we report on the outcome of a pilot study conducted to investigate the social mixing behavior of chronically ill people in a pilot contact survey (ICSOC study) in the provinces of Limburg and Antwerp in Belgium between January 2017 and April 2017. Eighteen recruited general practitioners actively distributed questionnaires and we retrieved a total of 99 questionnaires of which 21 were from participants with a chronic condition and 78 were from participants with an ILI. Fifty-three questionnaires were first questionnaires and 25 were follow-up questionnaires. Driven by the different conditions under study, we created various subgroups for comparison, distinguishing between absence or presence of a chronic conditions, having an ILI or not and paired information or not. A list of the included conditions is included in Supplementary Table 1.

This study aimed to quantify changes in social contact behavior resulting from seasonal influenza or chronic diseases. This pilot study was conducted to test the questionnaires and the feasibility of a large-scale contact survey. It also allows us to gain preliminary insight into the social mixing behavior in this patient cohort.

In the ICSOC pilot survey (see supplementary information), we observed a substantial reduction in the social mixing of NCD patients compared with healthy controls (Fig. 1). In the chronically ill a similar reduction in the social mixing as in healthy individuals upon an ILI was observed (Eames et al., 2012; Van Kerckhove et al., 2013), indicating that the nature of the overall reduction in social contacts is a feature characterizing their chronic disease, and the nature of this reduction is different from the reduced contacting upon an acute illness. Notwithstanding the limited size and the heterogeneity in the conditions that were included in this survey, our data indicate a similar impact on the social mixing behavior irrespective of the underlying disease. This presumably reflects that different NCDs have a similar impact on general health, mobility or behavior.

This decreased social mixing of patients with NCD has important implications. First, extrapolating mathematical models of social mixing data collected from predominantly healthy individuals to the NCD population is incorrect. The NCD population demonstrates substantially fewer social interactions and it remains to be established whether the distribution of these contacts among different age-groups is comparable to the healthy population. A large-scale contact survey, where the social interactions of different NCD disease entities are monitored in terms of distribution across age groups but also with respect to duration and intimacy will be instrumental to build a mathematical framework allowing the characterization of the spread of an infection in the NCD population and the impact of preventive policies. Secondly, the increased susceptibility to infection that is starting to emerge in literature represents an underestimation of the true susceptibility of the NCD population as their social mixing is reduced. Notably, the increased infectious risk is not uniform across different NCD disease entities, nor in terms of the type of infection and the pathogen, nor in terms of the height of the increased susceptibility. This is at least partially due to the different impact of the chronic disease on immune competence and specific immunological cell processes (as illustrated in Table 1), but it can also be a consequence of the disease as specific NCDs are associated with organ

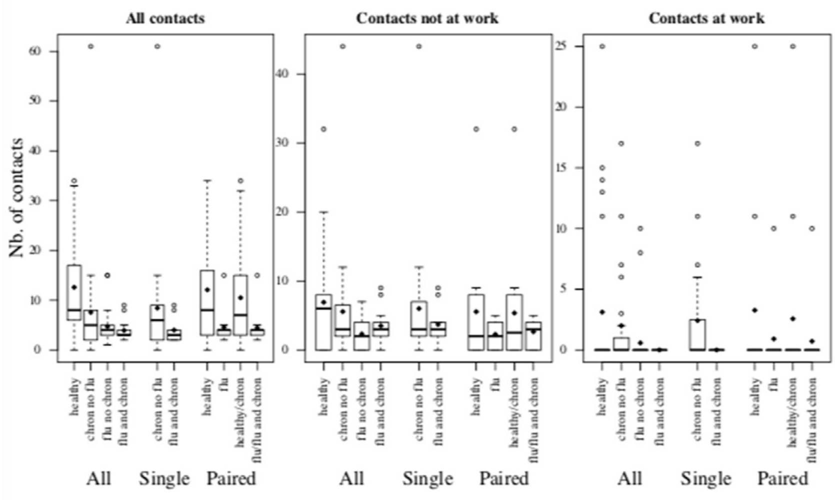

Fig. 1. Graphical comparison of the number of contacts. Panels show from left to right the box plots of all contacts including additional work contacts if applicable, the number of contacts without work contacts and the work contacts only. In each panel, the different groups are displayed where three main differentiations can be observed based on all data (first four boxes), based on the single data hence ignoring questionnaires available in both groups (fifth and sixth box) and based on the paired data (meaning we had filled in questionnaires in presence and absence of an ILI, i.e. last four boxes). The paired data either involves only those who had an ILI only and were recovered the second time (first two boxes) or includes those people who also had a chronic condition (last two boxes).

dysfunction and tissue damage that also contribute to susceptibility. For example, the lung function decline in COPD patients results in a reduced capacity to clear the lungs of bacteria, dust and air pollutants. The synergy of this physical inability together with the dysfunctional innate lung defense leads to increased susceptibility to infection (Sethi, 2010). Additionally, therapeutic interventions that aim to control disease manifestations can contribute to overall susceptibility.

Third, it is evident that the relation between the disease burden and its impact on social mixing may not be uniform for different disease entities. For example, the early stages of reduced kidney function are subclinical (Ishigami and Matsushita, 2019), so less social mixing is not expected (GBD Chronic Kidney Disease Colaboration, 2020). In contrast, in COPD and heart failure patients a more linear decrease in mobility upon progressive disease can be anticipated. Therefore, assessing disease burden (disease stage and activity) and using a limited set of disease entities in the survey is an important determinant of a large-scale NCD-survey.

Fourth, the NCD population differs not only in the quantity of their social interaction but also qualitatively in their contacts with the healthy population. NCD patients require more medical care and contact with healthcare workers imposes a higher risk for infection as these contacts are at greater risk of acquiring and spreading infections due to the nature of their work (Huttunen & Syrjänen, 2014; Jiang et al., 2018; Sydnor & Perl, 2014). Given their healthcare requirements, the relative proportion of contacts that pose an elevated risk because of their location, duration or intimacy will differ from the healthy population. An illustrative example of this concept are patients with end-stage renal disease (ESRD) as their renal dysfunction requires renal replacement therapy. Irrespective of the type of dialysis the procedure is associated with a high mortality and infection remains a major cause of death (Saeedi et al., 2019). Finally, as some specific NCDs are associated with a lower vaccination response and specific types of infection, tailored prophylactic pharmaceutical interventions may be required for such at risk populations. This may include tailored vaccination strategies and/or prophylactic treatment with antivirals or antibiotics. Additionally, we also anticipate that tailored non-pharmaceutical strategies (such as changing the dialysis environment) could be highly effective.

The intimidating relationship between the SARS-CoV-2 pandemic and NCD underscores the importance of infection as a key determinant in the management of NCD. Although it is common to approach chronic and infectious diseases as having completely distinct etiologies, there is an increasing appreciation that the interplay between chronic disease and infection harbors underexplored preventive opportunities to alter non-communicable disease. Our demonstration that less social mixing occurs regardless of the chronic condition, taken together with epidemiologic observations of increased susceptibility to specific infections, warrants disease-specific contact surveys to address how the burden of the disease associates with the social contact behavior and the risk of infection. We anticipate that such knowledge will enable disease-specific policies aimed at preventing infection in the NCD population and provide new ways to leverage healthcare technologies and improve healthcare procedures, the relevance of which is illustrated by the grim fate of the NCD population during the SARS-CoV2 pandemic.

Table 1
The importance of infection in diabetes, chronic kidney disease and chronic obstructive pulmonary disease.

Chronic illness	Diabetes	Chronic kidney disease (CKD)	Chronic obstructive pulmonary disease (COPD)
Frequency in the population	9.3% of the population (Saeedi et al., 2019)	9.1% of the population (Reddy et al., 2019)	12.16% of the population (Varmaghani et al., 2019)
impact of the disease on society	631 hospitalizations/1000 person years (Comino et al., 2015)* 6.8% of overall mortality in the population 7th leading cause of death worldwide	350 hospitalizations/1000 person years (Schrauben et al., 2020) * 1.7% of overall mortality in the population 13th leading cause of death worldwide	307 hospitalizations/1000 person years (Harries et al., 2017) * 4.8% of overall mortality in the population 5th leading cause of death worldwide
Impact of infection on disease outcome	3rd cause of hospitalization (16%) 2nd cause of mortality	2nd cause of hospitalization (21%) (Yang, Chnag, et al., 2020) 2nd cause of mortality	2nd cause of hospitalization 4th cause of mortality Infection is a trigger for the disease Infection is a trigger for exacerbation of the disease.
Impact of disease on infectious risk	Pneumonia: HR 1.3–1.5 (Casqueiro et al., 2012) TBC: HR 1.5–3.0	Risk of infection correlates quantitatively with EGFR and albuminuria (Yang, Chnag, et al., 2020)	Pneumonia: (Lange, 2009; Wackerhausen & Hansen, 2012) TBC: HR 2.42–4.08 Infectious risk is further increased by treatment (e.g. inhaled corticosteroids)
Typical infections	Respiratory tract infections Urinary tract infections Bacteremia	Broadly increased susceptibility (bacteria, viral infection)	Only risk of respiratory tract infections is increased (both bacterial and viral). No evidence of increased susceptibility to other infection
Immune mechanisms that are compromised	Impaired neutrophil and phagocyte function Reduced IL-response	Reduced lymphocyte (B and CD4 T cell) counts Reduced T cell responses Reduced phagocytosis	Compromised mucocilliary barrier and inappropriate endothelial responses
Impact of disease on burden of infection	DM patients have a 6-fold increased risk of hospital admittance after influenza	Strong quantitative correlation between EGFR or albuminuria and the risk of hospitalization	Risk of hospital admittance is proportional to COPD disease stage
Predicted impact of the disease on contact behavior	Impact on social mixing is presumably mainly determined by the comorbidities and complications (e.g. cardiovascular complications, diabetic nephropathy)	Correlation of the extent of the disease with overall immobility and social mixing behavior, but there is a threshold as mildly reduced EGFR is subclinical and no impact on social mixing is expected The necessity of dialysis in patients with ESRD has an impact the social contact behavior in ESRD patients	Correlation of the extent of the disease with overall mobility and overall social mixing behavior
Vaccination effectivity	Influenza vaccination strategies succeed at reducing all-cause mortality in diabetics To be determined whether all subgroups display vaccination efficacy	ESRD patients display reduced vaccination response, a faster decline of antibodies post-vaccination and a lack of effect of influenza vaccination on influenza/ pneumonia hospitalization	Vaccination response is intact in COPD patients Vaccination results in significant health benefit, fewer infections, fewer hospitalizations, fewer exacerbations and reduced mortality.

• As a reference: 92 hospitalizations/1000 person years (all ages) and 214 hospitalizations/1000 person years (>65 years) in the general population.
Abbreviations: EGFR (estimated glomerular filtration rate); HR (Hazard ratio), ESRD (end-stage renal disease).

CRediT authorship contribution statement

J. Vanderlocht: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Conceptualization. **S. Møgelmose:** Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **K. Van Kerckhove:** Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **P. Beutels:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **N. Hens:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have read the journal's policy concerning competing interests. JV is, besides his employment at the Hasselt University, part of the investment team of Bioqube Ventures and a consultant for BetaCell NV. Nor Bioqube Ventures, nor BetaCell NV was involved in this work, nor does it prosper financially as a result of the current study. NH reports grants from GSK Biologicals, Pfizer, Merck and J&J, outside the submitted work. The other authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2024.05.002.

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