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Investigating the relationship between interventions, contact patterns, and SARS-CoV-2 transmissibility

Filippo Trentini[a,b,c,*], Adriana Manna[a,d], Nicoletta Balbo[a,e], Valentina Marziano[c], Giorgio Guzzetta[c], Samantha O'Dell[f], Allisandra G. Kummer[f], Maria Litvinova[f], Stefano Merler[c], Marco Ajelli[f], Piero Poletti[c], Alessia Melegaro[a,b,e,**]

[a] *Dondena Centre for Research on Social Dynamics and Public Policy, Bocconi University, Milan, Italy*
[b] *Covid Crisis Lab, Bocconi University, Italy*
[c] *Center for Health Emergencies, Bruno Kessler Foundation, Trento, Italy*
[d] *Department of Network and Data Science, Central European University, Wien, Austria*
[e] *Department of Social and Political Sciences, Bocconi University, Milan, Italy*
[f] *Laboratory for Computational Epidemiology and Public Health, Department of Epidemiology and Biostatistics, Indiana University School of Public Health, Bloomington, IN, USA*

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ABSTRACT

Background: After a rapid upsurge of COVID-19 cases in Italy during the fall of 2020, the government introduced a three-tiered restriction system aimed at increasing physical distancing. The Ministry of Health, after periodic epidemiological risk assessments, assigned a tier to each of the 21 Italian regions and autonomous provinces. It is still unclear to what extent these different sets of measures altered the number of daily interactions and the social mixing patterns.

Methods and findings: We conducted a survey between July 2020 and March 2021 to monitor changes in social contact patterns among individuals in the metropolitan city of Milan, Italy, which was hardly hit by the second wave of the COVID-19 pandemic. The number of daily contacts during periods characterized by different levels of restrictions was analyzed through negative binomial regression models and age-specific contact matrices were estimated under the different tiers of restrictions. By relying on the empirically estimated mixing patterns, we quantified relative changes in SARS-CoV-2 transmission potential associated with the different tiers.

As tighter restrictions were implemented during the fall of 2020, a progressive reduction in the mean number of daily contacts recorded by study participants was observed: from 15.9 % under mild restrictions (yellow tier), to 41.8 % under strong restrictions (red tier). Higher restrictions levels were also found to increase the relative contribution of contacts occurring within the household. The SARS-CoV-2 reproduction number was estimated to decrease by 17.1 % (95 %CI: 1.5–30.1), 25.1 % (95 %CI: 13.0–36.0) and 44.7 % (95 %CI: 33.9–53.0) under the yellow, orange, and red tiers, respectively.

Conclusions: Our results give an important quantification of the expected contribution of different restriction levels in shaping social contacts and decreasing the transmission potential of SARS-CoV-2. These estimates can find an operational use in anticipating the effect that the implementation of these tiered restriction can have on SARS-CoV-2 reproduction number under an evolving epidemiological situation.

1. Introduction

During the COVID-19 pandemic, one of the main strategies used by governments to reduce SARS-CoV-2 transmission has been the introduction of non-pharmaceutical interventions to favor physical distancing. When a second wave of COVID-19 started spreading in Italy in the fall of 2020, the government progressively enhanced measures aimed at increasing physical distancing (Official Gazette of the Italian Republic, 2020a, 2020b, 2020c, 2020d). To better respond to a geographically heterogeneous increase of the number of COVID-19

* Correspondence to: Dondena Centre for Research on Social Dynamics and Public Policy, Bocconi University, Via Roentgen 1, 20141 Milan, Italy.
** Corresponding author at: Department of Social and Political Sciences, Bocconi University, Milan, Italy.
E-mail addresses: filippo.trentini@unibocconi.it (F. Trentini), alessia.melegaro@unibocconi.it (A. Melegaro).

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cases, a three-tiered restriction system was introduced on November 6, 2020. Since then, every week, a tier was assigned to each of the 21 Italian regions and autonomous provinces by the Ministry of Health after an epidemiological risk assessment based on a combination of quantitative indicators, such as the estimated level of transmission and the burden on the healthcare system (Official Gazette of the Italian Republic, 2020d). The sets of measures adopted in the three tiers were labeled according to a color scheme: yellow, orange, and red, corresponding to increasing levels of restrictions. These included the reinforcement of distance learning in primary and secondary schools, as well as the introduction of restrictions of individuals' mobility ranging from a ban on inter-regional movements to a stay-home mandate for the entire day (Manica et al., 2021).

Several studies conducted during the COVID-19 pandemic have quantified mixing patterns under different non-pharmaceutical interventions, highlighting the dramatic decrease of individuals' contact rates with respect to pre-pandemic levels (Strategy and Policy Working Group for NCIP Epidemic Response, 2020; Zhang et al., 2020; Feehan and Mahmud, 2021; Kiti et al., 2021; Gimma et al., 2022; Latsuzbaia et al., 2020; Jarvis et al., 2020; Zhang et al., 2021; Del Fava et al., 2021; Quaife et al., 2020; Liu et al., 2021; Backer et al., 2021). However, to what extent the tiered restrictions adopted in Italy have altered daily interactions and mixing patterns has yet to be quantified. A fundamental question that is still open is whether the change of mixing patterns associated to implemented restrictions can be used to anticipate the effect of a given intervention on SARS-CoV-2 transmissibility.

The present study aims at investigating the changes in number of daily contacts and mixing patterns linked to the different levels of non-pharmaceutical interventions adopted by the Italian government during the second wave of the COVID-19 pandemic, and to examine their impact on SARS-CoV-2 transmission. To this aim, we performed a contact survey in the metropolitan city of Milan, Italy, between July 2020 and March 2021. The survey collected information on the number and type of daily contacts made by study participants, over a period when interventions of different intensity were in place. This data allowed us to assess the impact of the adopted restrictions on human mixing patterns and, through the use of mathematical modeling, estimate their effect on SARS-CoV-2 reproduction number.

2. Methods

The study was conducted between July 10, 2020, and March 31, 2021, in the metropolitan city of Milan, in Lombardy Region of Italy. Data were collected in collaboration with Centro Medico Santagostino (CMS), a private healthcare center that is part of the National Health Service.

2.1. Tiered restrictions

During the period of data collection, the study population underwent all the restriction levels defined by the Italian tiered restrictions system (Table S1 in Appendix). In the baseline analysis, we assimilated the pre-tier period - between October 26 and November 5, 2020 - to the yellow tier, due to the similar restrictions preventively introduced by the Lombardy region with a decree of October 16, 2020 (Decree of the Lombardy, 2020). In Appendix, we present the results obtained by considering this period separately and labeling it with a different color: green. The period between July 10, 2020, and October 25, 2020, is hereafter denoted as white tier.

2.2. Study design and data collection

Participants were selected among individuals who booked an appointment to undergo IgG serological SARS-CoV-2 testing at CSM on a complete voluntary basis. While booking the serological test, individuals were invited to participate in the study and, after acceptance, to fill in an online questionnaire on their social behavior (see Appendix). Recruitment of participants was conducted irrespectively to their potential participation to other studies or to their potential clinical condition. Study participants were not followed up in time and no information was recorded on the reason why they were seeking an IgG test. Serological testing was not part of any policy undertaken by the health authorities to control the transmission and, differently from PCR tests, the results of a serological test were not considered to apply different measures (e.g., isolation) to negative/positive individuals. Informed consent was sought for individuals aged 18 years or more, and from a parent or legal guardian for underage individuals. Only 696 (39 %) of individuals who were accepted to participate in the contact study eventually underwent the serological test, among those, 462 (66 %) received the result before filling in the contact questionnaire.

The questionnaire was composed of two parts: (i) we collected key socio-demographic information on the participant (age, gender, occupational status, household size, and age of their household members); (ii) we recorded information on the number and characteristics of the social interactions (i.e., *contacts*) that the participant experienced during the day preceding the questionnaire. The questionnaire was implemented through an online platform. Data were anonymized by CMS before conducting the analysis of the collected records.

To make our results comparable with the literature on contact patterns for respiratory infectious diseases (Hoang et al., 2019; Mousa et al., 2021), we used a widely adopted definition of contact: a *contact* was defined as a physical interaction or a two-way conversation of at least five words in the physical presence of another person. The same definition of contact was used in the only diary-based contact study conducted in Italy before the COVID-19 pandemic where the age of both the contact and contacted individuals were recorded (Mossong et al., 2008). For each reported contact, the following information was recorded: (i) the sex of the contacted person, (ii) the age (either precise or range) of the contacted person, (iii) if the contact happened indoor or outdoor, (iv) the frequency at which the contact usually happens (more than once a day, once a day, more than once a week, once a week, less than once a week – occasional contact), (v) if the experienced contact included a physical interaction or not (e.g.; hand shake, hug), (vi) the relationship between the study participant and the contacted person (household member, other relative, classmate, colleague, friend/partner, other), and (vii) the location where the contact occurred (home, school, workplace, public transportations, or other). Ethical approval for this study was waived by the Ethical Review Board of Bocconi University, Milan.

2.3. Descriptive analysis of contacts

We analyzed the frequency distribution of daily contacts of study participants for a set of covariates, including their age, sex, employment status, a dichotomous variable that indicates whether the study participant had a contact with a SARS-CoV-2 positive case in the three weeks preceding the interview, and the restriction tier at the time of interview. Repeated encounters reported with the same individual counted as one contact only, following the same approach used elsewhere (Melegaro et al., 2017; Trentini et al., 2021).

To assess differences across multiple groups, we used one-way ANOVA, followed by post-hoc Tukey test. Estimated 95 % confidence intervals and p-values are based on the Studentized range statistic and the Tukey's 'Honest Significant Difference' method.

We used negative binomial regressions to estimate the mean number of daily contacts as a function of the covariates. Negative binomial regressions were preferred over Poisson regressions given evidence of overdispersion (variance > mean), and a significant likelihood ratio ($P < 0.05$) for the overdispersion parameter. Separate regressions were applied to the overall number of reported daily contacts and to those that occurred within and outside the participant's household.

2.4. Contact patterns

We assigned a tier to each participant based on the one assigned to the Lombardy region at the time the interview was conducted. We analyzed the mean number of daily contacts reported by respondents after grouping by age (one age group for individuals between 0 and 20 years of age, five 10-year age groups from 20 to 69 years, and one for individuals aged 70 years or older) and by tier (white, yellow, orange, and red). We estimated contact matrices where each element c_{ij} represents the mean number of daily contacts study participants in age class *i* have with individuals of age class j, considering both physical and non-physical contacts and adjusting for reciprocity as in (Melegaro et al., 2017; Trentini et al., 2021) (see the Appendix for further details).

To correct for the selection bias in our sample, we performed 1000 bootstrapped samples by sampling with replacement a number of interviews equal to the original sample size in each tier and choosing the age of the participant with probability proportional to the age distribution in the metropolitan city of Milan (Zhang, Jun 26 et al., 2020; Trentini et al., 2021).

2.5. Estimation of reproduction number

The reproduction number associated with each tier was estimated by using the Next Generation Matrix (NGM) approach applied to an age-structured SIR transmission model where interactions between individuals of different ages are defined by the contact matrices derived in this study (Diekmann et al., 1990). A generation time of 6.6 days was assumed to reflect the serial interval of COVID-19 observed in the region at the beginning of the pandemic (Cereda et al., 2021; Guzzetta et al., 2020). The NGM was computed under the illustrative condition of a fully susceptible population. Heterogeneous susceptibility to infection at different ages as estimated in (Hu et al., 2021) was explored as a sensitivity analysis.

To evaluate relative changes in the transmission potential determined by the different tiers, we considered a baseline NGM, computed by using contact records collected before the introduction of tighter restriction in the Lombardy region (between July 13, 2020, and October 25, 2020). The reduction in transmission led by mild, moderate, and strong restrictions (yellow, orange, and red tiers, respectively) was then defined as one minus the ratio between the dominant eigenvalue of the

Table 1
Sample description and mean number of daily contacts per person as recorded under different tiers.

Variables	Overall		White tier		Yellow tier		Orange tier		Red tier	
	Sample size	Mean (95 % CI)	Sample size	Mean (95 % CI)	Sample size	Mean (95 % CI)	Sample size	Mean (95 % CI)	Sample size	Mean (95 % CI)
Overall	1683 (100 %)	4.54 (4.32–4.76)	1025 (61 %)	5.09 (4.81–5.37)	292 (17 %)	4.28 (3.69–4.87)	160 (10 %)	3.55 (2.96–4.14)	206 (12 %)	2.96 (2.49–3.43)
Age										
0–19	42 (2 %)	5.69 (4.01–7.37)	28 (3 %)	6.64 (4.18–9.11)	6 (2 %)	3.83 (1.69–5.98)	4 (2 %)	4.25 (2.73–5.77)	4 (2 %)	3.25 (1.25–5.25)
20–29	364 (22 %)	4.34 (3.95–4.73)	243 (24 %)	4.79 (4.28–5.3)	59 (2 0%)	3.81 (3.1–4.53)	33 (21 %)	2.48 (1.46–3.51)	29 (14 %)	3.83 (2.46–5.19)
30–39	560 (33 %)	4.27 (3.9–4.63)	383 (37 %)	4.69 (4.24–5.13)	82 (28 %)	3.67 (2.73–4.61)	34 (21 %)	2.94 (2.01–3.87)	61 (30 %)	3.16 (2.1–4.23)
40–49	325 (19 %)	5.34 (4.68–6)	206 (20 %)	5.79 (5–6.59)	48 (16 %)	5.81 (3.26–8.36)	32 (20 %)	4.53 (2.82–6.24)	39 (19 %)	3.03 (1.87–4.18)
50–59	224 (13 %)	4.71 (4.18–5.24)	108 (11 %)	5.51 (4.81–6.21)	42 (14 %)	5.12 (3.49–6.75)	27 (17 %)	4.37 (2.71–6.03)	47 (23 %)	2.68 (1.89–3.47)
60–69	112 (7 %)	4.11 (3.34–4.87)	44 (4 %)	5.5 (4.35–6.65)	32 (11 %)	3.94 (2.26–5.61)	16 (10 %)	3.31 (0.88–5.75)	20 (10 %)	1.95 (1.08–2.82)
70+	56 (3 %)	3.32 (2.57–4.07)	13 (1 %)	3.23 (2.3–4.16)	23 (8 %)	3.52 (2.28–4.76)	14 (9 %)	3.79 (1.58–6)	6 (3 %)	1.67 (0.23–3.1)
Sex										
Female	978 (58 %)	4.6 (4.34–4.87)	593 (58 %)	5.21 (4.86–5.56)	174 (60 %)	4.11 (3.53–4.69)	94 (59 %)	3.36 (2.56–4.16)	117 (57 %)	3.27 (2.6–3.95)
Male	705 (42 %)	4.46 (4.08–4.83)	432 (42 %)	4.92 (4.46–5.39)	118 (40 %)	4.53 (3.33–5.74)	66 (41 %)	3.82 (2.93–4.7)	89 (43 %)	2.55 (1.93–3.17)
Employment status										
Employed	1317 (78 %)	4.66 (4.4–4.91)	834 (81 %)	5.14 (4.82–5.45)	219 (75 %)	4.44 (3.7–5.18)	109 (68 %)	3.63 (2.87–4.39)	155 (75 %)	3.1 (2.51–3.69)
Inactive	141 (8 %)	3.63 (3–4.27)	53 (5 %)	5 (3.91–6.09)	38 (13 %)	3.55 (2.12–4.99)	26 (16 %)	2.88 (1.58–4.19)	24 (12 %)	1.54 (0.97–2.11)
Student	157 (9 %)	4.82 (4.16–5.48)	98 (10 %)	5.15 (4.19–6.11)	24 (8 %)	4.38 (3.17–5.58)	18 (11 %)	4.5 (2.79–6.21)	17 (8 %)	3.88 (2.87–4.89)
Unemployed	68 (4 %)	3.56 (2.71–4.41)	40 (4 %)	4.08 (2.77–5.38)	11 (4 %)	3.36 (1.63–5.1)	7 (4 %)	2.29 (0.24–4.33)	10 (5 %)	2.6 (0.81–4.39)
Household size										
At most 2	1070 (64 %)	3.74 (3.48–4)	634 (62 %)	4.27 (3.94–4.59)	204 (70 %)	3.71 (2.95–4.47)	93 (58 %)	2.48 (1.8–3.17)	139 (67 %)	2.21 (1.63–2.79)
3	295 (18 %)	5.23 (4.68–5.79)	190 (19 %)	5.42 (4.68–6.16)	33 (11 %)	6.3 (4.49–8.12)	36 (22 %)	4.69 (3.25–6.14)	36 (17 %)	3.81 (2.87–4.74)
4	256 (15 %)	6.46 (5.92–7)	160 (16 %)	7.3 (6.54–8.06)	50 (17 %)	4.88 (4.18–5.58)	22 (14 %)	5.36 (3.7–7.03)	24 (12 %)	5.17 (4.03–6.3)
5+	62 (4 %)	7.18 (6.17–8.19)	41 (4 %)	7.61 (6.3–8.92)	5 (2 %)	8.2 (0.04–16.36)	9 (6 %)	5.56 (3.75–7.36)	7 (3 %)	6 (4.59–7.41)
Contact with a positive case within three weeks since interview date										
No	1569 (93 %)	4.63 (4.4–4.85)	981 (96 %)	5.15 (4.85–5.44)	255 (87 %)	4.35 (3.69–5.01)	149 (93 %)	3.56 (2.96–4.17)	184 (89 %)	3.09 (2.58–3.6)
Yes	114 (7 %)	3.39 (2.74–4.05)	44 (4 %)	3.82 (2.69–4.95)	37 (13 %)	3.81 (2.61–5.01)	11 (7 %)	3.36 (0.24–6.49)	22 (11 %)	1.86 (1.1–2.63)

NGM computed using contact patterns estimated for the considered tier and the one associated with the baseline NGM.

3. Results

3.1. Description of study participants

A total of 1683 individuals were interviewed. Due to the constrained nature of the study, female individuals (58.1 %) and adults between 20 and 64 years of age (91.0 %) were oversampled, as shown in Figs. S1 and S2 in the Appendix. The median age of participants was 37 years (IQR 30–48). Participants under 20 years of age and above 64 years of age represent the 2.5 % (42 participants) and the 6.5 % (110 participants) of sample, respectively. Overall, 1025 participants (60.9 %) were interviewed before the introduction of the tiered restrictions system (white tier), 292 while in the yellow tier (17.3 %), 160 while in the orange tier (9.5 %), and 206 while in the red tier (12. 2%). Fig. S3 in the Appendix shows the number of interviews and the number of notified cases along with the restrictions in the study period. Most participants were employed (78.3 %), 9.3 % were students, and 12.4 % either inactive or unemployed; most study participants (61.4 %) were cohabiting with one individual. 114 study participants (6.8 %) reported to have had a contact with someone who tested positive for SARS-CoV-2 in the three weeks before the interview date. Descriptive statistics are reported in Table 1.

3.2. Contacts

The introduction of the tiered restriction system strongly influenced the number of social interactions of study participants of all age classes (see Fig. 1A and Table 1). The mean number of daily contacts reported in the white tier was 5.09 (95 %CI: 4.81–5.37). Compared to what was observed in white tier, this quantity decreased by 0.81 (95 % CI: 0.04–1.58, p-value for a post-hoc Tukey test on the mean differences = 0.036), 1.54 (95 %CI: 0.55–2.53, p-value $<$ 0.001) and 2.13 (95 %CI: 1.24–3.01, p-value $<$ 0.001) during the yellow, orange, and red tiers, respectively. No significant differences in the mean number of daily contacts were found between yellow and orange tiers (p-value = 0.354) and between orange and red tiers (p-value = 0.604). However, a significant difference was found between mean number of daily contacts reported in the yellow and the red tier (4.28 vs 2.96; p-value = 0.007). Compared to contacts observed before the introduction of the tiered restriction system, this corresponds to a relative reduction in the overall number of daily contacts of 15.9 %, 30.2 % and 41.8 % for mild, moderate, and strong restrictions, respectively.

Our sample is not representative of the age distribution of the metropolitan city of Milan (see Appendix), mainly due to an under-representativeness of children and adolescents across all periods and of elderly in the reference period. Therefore, we adopted the bootstrap procedure described in the methods to correct for this bias. Resulting estimates for the mean of daily contacts occurring in the different tiers are not significantly different from the crude estimates obtained from the original sample (5.15 95 %bCI: 4.72–5.62; 4.28 95 %bCI: 4.72–5.62; 3.78 95 %bCI: 3.45–4.12; and 2.76 95 %bCI: 2.52–3.03 for the white, yellow, orange, and red tiers respectively). The overall number of contacts estimated through the bootstrap procedure (3.99 95 %bCI: 3.80–4.18) was slightly lower compared to what resulting from the original sample (4.54 95 %CI: 4.32–4.76).

As shown in Fig. 1B, the most marked differences in the average number of daily contacts were observed among individuals between 40 and 69 years of age, with the mean number of daily contacts decreasing from 5.79 (95 %CI: 5.0–6.59) for 40–49 years old, 5.51 (95 %CI: 4.81–6.21) for 50–59 years old and 5.5 (95 %CI: 4.35–6.65) for 60–69 years old while in the white tier to 3.03 (95 %CI: 1.87–4.18), 2.68 (95 % CI: 1.89–3.47) and 1.95 (95 %CI: 1.08–2.82), respectively, while in the red tier. Individuals aged 20–29 years were least affected by the tier change. Inactive individuals showed a higher reduction of contacts than students and employed individuals (69.2 % reduction from the white to red tiers vs. 24.7 % and 39.7 %). Individuals belonging to larger households reported a higher number of daily contacts in all tiers. While in the red tier, the mean number of reported daily contacts was just above the number of individuals cohabiting with the study participant. Among all study participants, 114 (6.8 %) had a contact with a SARS-CoV-2 positive case within three weeks since the interview date. These individuals reported a 26.6 % reduction of the mean number of daily contacts compared to other participants (3.39 vs 4.63).

We found a decrease of the mean number of daily contacts with occasional peers (contacts generally occurring less than once in a week) reported by study participants in the orange and red tiers (see Fig. 1A). The mean daily number of contacts recorded outdoors also shows a progressive decreasing trend. While outdoor contacts accounted for about 15–20 % of all contacts in period preceding the introduction of the tiered restrictions (August and September 2020), their contribution became less than 10 % between October and December 2020.

To better disentangle the role of the tiered restrictions in shaping the number of daily interactions, a negative binomial regression was applied to the number of daily contacts recorded by the study participants, adjusting for their sex, age, household size, employment status, and serological status. The same model was also separately applied to contacts recorded with household members and with non-household members. The resulting estimates (see Fig. 2) suggest that, compared to what was observed under the white tier, the number of daily contacts reported by the study participants decreased by 11.49 % (95 %CI: 0.48–21.20) under the yellow tier, by 31.69 % (95 %CI: 20.30–41.37) under the orange tier, and by 41.28 % (95 %CI: 32.46–48.90) under the

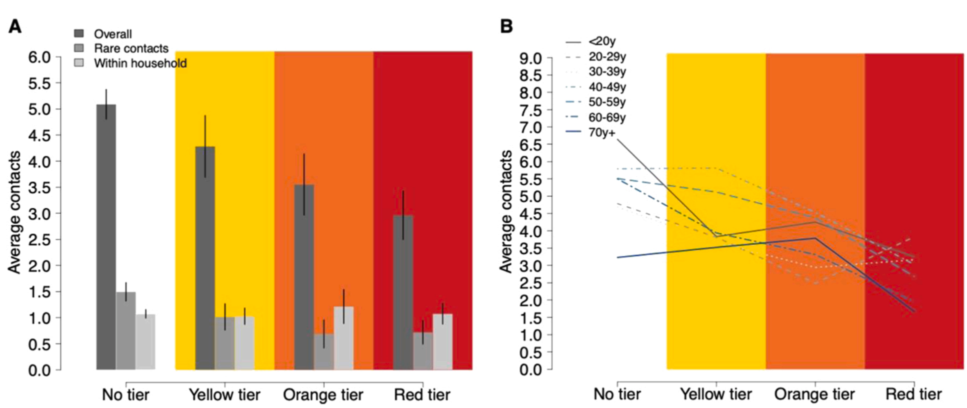

Fig. 1. A. Bars represents the mean number of daily contacts reported by the study participants in different tiers, stratified by type of contact: overall, rare (less than once a week) and within household. Gray lines represent 95 % confidence intervals. B. Different lines represent the age-specific mean number of daily contacts in the different tiers.

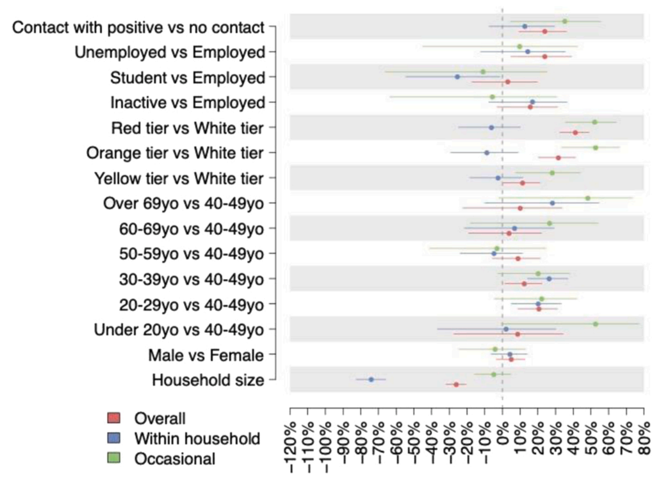

Fig. 2. Percentage reduction of the daily number of daily contacts reported by study participants with respect to different covariates of interest, obtained as 1 minus the exponentiated coefficients estimated by a negative binomial regression applied to the overall number of daily contacts (overall; red dots), the number of daily contacts occurred less than once a week (occasional contacts; green dots) and with household members (in-household; blue dots). Lines represent 95 % confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

red tier (Fig. 2). Although the number of daily contacts with household members was slightly higher in the orange and red tiers (Fig. 1A), these differences were not significant (reference: white tier; p-values of coefficients for yellow, orange, and red tiers: 0.75, 0.35 and 0.48, respectively). In contrast, the mean number of contacts with occasional peers (i.e., contacts occurring less than once a week) significantly decreased by 28.29 % (95 %CI: 7.52–44.11; p-value: 0.024), 52.70 % (95 %CI: 33.36–66.19; p-value: 0.001) and 52.13 % (35.51–64.28; p-value <0.001) in the yellow, orange, and red tiers, respectively (Fig. 2). Estimated model coefficients and relative confidence intervals are shown in Table S3 of the Appendix.

Figs. S4 and S5 in the Appendix show the results of a sensitivity analysis that considers the pre-tier period (October 26–November 5) separate from the yellow tier. The resulting estimates are in line with those obtained in the baseline analysis. A similar reduction in the average number of daily contacts was found for the yellow tier and the pre-tier period associated with the implementation of preventive restrictions in Lombardy. However, when these two periods are considered separately, the former shows a broader variability around the estimated reduction.

3.3. Age specific mixing patterns under different tiers

The analysis of contact patterns by age shows that higher restriction levels could markedly reduce both the number of intergenerational contacts had by the elderly (>60 years of age) and the intensity of assortative mixing in younger individuals. In children and adolescents (< 20 years of age), the latter phenomenon is likely related to the reinforcement of distance learning under more restrictive tiers. Beyond reducing the overall number of social interactions, higher restrictions levels were found to increase the relative contribution of contacts between young adults (aged 30–50 years) with individuals of similar age and with individuals younger than 10 years of age. This result is likely related to interactions occurring within the household between partners, and between parents and their children (Fig. 3A–D).

3.4. Impact of restrictions on SARS-CoV-2 transmissibility

By comparing the transmission potential associated with contact patterns measured under different tiers, we found that - compared to what was expected before the introduction of the tiered system – the SARS-CoV-2 reproduction number is expected to decrease by 17.1 % (95 %CI: 1.5–30.1), 25.1 % (95 %CI: 13.0–36.0) and 44.7 % (95 %CI: 33.9–53.0) under the yellow, orange, and red tiers, respectively (see Fig. 3E). These estimates are consistent with those obtained from the

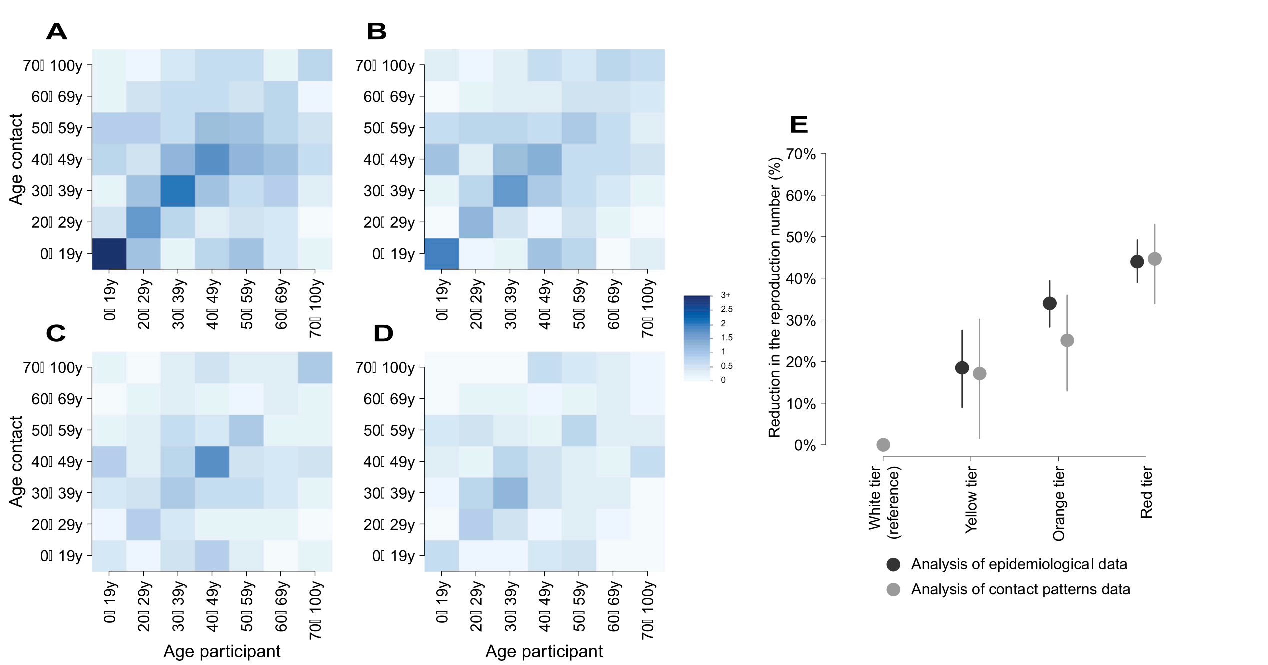

Fig. 3. A–D) Average contact matrix representing the mean number of daily contacts reported by a participant in the age group *i* with individuals in the age group *j* under the white (A), the yellow (B), the orange (C) and the red tiers (D). E) Mean percentage reduction of SARS-CoV-2 reproduction number ascribable to the observed change of contact patterns (gray dots) and as estimated in (Manica et al., 2021) by analyzing the time series of the SARS-CoV-2 net reproduction number in Italy between October 30 and November 25, 2020 (black dots), under the yellow, the orange and the red tiers with respect to the white tier. Vertical lines represent 95 % confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

analysis of the Italian epidemiological surveillance (Manica et al., 2021), where the relative reduction of the reproduction number was estimated at 18.5 % (95 %CI: 9.0–27.5) under yellow tier restriction, 34.0 % (95 % CI: 28.3–39.4) under orange tier restrictions and 44.0 % (95 %CI: 39.1–49.2) under red tier restrictions (see Fig. 3E).

As shown in Fig. S6 of the Appendix, the obtained estimates are robust with respect to the assumption of age-specific susceptibility to SARS-CoV-2 infection.

The estimated contact matrices and reductions in the reproduction number of SARS-CoV-2 when considering separately the yellow tier and the pre-tier period associated with the implementation of preventive restrictions in Lombardy are in line with results obtained in the baseline analysis (see Fig. S5 of theAppendix). Again, in this case, the estimate for the reduction in the reproduction number in the yellow tier shows much higher variability than that of the pre-tier period associated with preventive restrictions.

4. Discussion

The analyzed data was collected from a contact survey conducted in the metropolitan city of Milan between July 2020 and March 2021 through online interviews and encompasses all possible levels of restrictions coded by the tiered system introduced in Italy in November 2020. The collected data was used to provide estimates of the average differences in the number of daily contacts and mixing patterns linked to the changes of non-pharmaceutical interventions as well as their potential impact on SARS-CoV-2 transmission. We found that the number of daily contacts per participant was significantly higher in the period preceding the introduction of the tiers (reference period) when all social distancing measures, except for the mandate of using PPE (personal protective equipment) in closed spaces, were temporally relaxed despite an improved epidemiological situation compared to spring of 2020. The estimated number of contacts in that period is considerably lower than pre-pandemic estimates: 5.09 (4.81–5.37) vs. 19.8 (SD = 12.3) found in the POLYMOD study in 2007 (Mossong et al., 2008). This approximately 4-fold reduction is consistent with evidence from the UK (Gimma et al., 2022; Jarvis et al., 2020) and from different Chinese provinces (Zhang, Jun 26 et al., 2020; Zhang et al., 2021).

As tighter restrictions were implemented during the fall of 2020, a progressive reduction in the mean number of daily contacts recorded by study participants was observed: 15.9 % under mild restrictions (yellow tier), 30.2 % under moderate restrictions (orange tier) and 41.8 % under strong restrictions (red tier). A further validation of our estimates of contact patterns come from the comparison with Google mobility data (Google, 2020). We found a significant positive correlation between the mean number of daily contacts over time and the weekly changes in time spent in retail and recreation activities, grocery and pharmacy, and parks and transit stations; and a negative correlation with time spent in residential places (see Appendix).

We estimated that the impact of contact patterns on transmission can be quantified with a decrease of 17.1 %, 25.1 % and 44.7 % in the SARS-CoV-2 reproduction number in the yellow, orange, and red tiers, respectively. A retrospective study analyzing SARS-CoV-2 epidemiological data has quantified the relative reduction of the net reproduction number associated to the adoption of different tiers between October and November 2020 (Manica et al., 2021). Remarkably, the latter estimates compare well with what we have obtained in the present study, which relies on contact patterns data only (i.e., without any direct knowledge of the actual transmission patterns). First, this supports the relevance of mixing patterns as a predictor of infection transmission dynamics. Second, should these tiered restrictions be adopted again in the future and assuming (i) a similar compliance of the population to the policy and (ii) a similar response of the population to changes occurred in the perceived risks, our estimated change in mixing patterns could allow for anticipating the impact of these interventions. Moreover, while inputting the estimated contact reduction in an epidemic model can provide insights on the impact of the implemented interventions for any epidemiological situation (i.e., the model can simulate a certain level of vaccination, infection prevalence, etc.), the same may not be true for reductions of the reproduction numbers estimated under a specific epidemiological situation (Manica et al., 2021; Davies et al., 2021). It should be noted that our findings rely on the assumption of a generation time of 6.6 days as estimated for the ancestral lineage during the early phase of the pandemic in Italy (Cereda et al., 2021). Despite the fact that the generation time could be affected by interventions in place to curb the epidemic (McAloon et al., 2022; Ali et al., 2020), studies conducted in Italy showed limited differences between the intrinsic generation times associated with different lineages over the course of the pandemic: 6.0 days for the Alpha variant (Manica et al., 2022b), 6.6 days for Delta (Manica et al., 2022b), and 6.8 days for Omicron (Manica et al., 2022a).

When interpreting our results, the following limitations should be considered. In particular, the analyzed sample is affected by a strong selection bias. Indeed, study participants were enrolled among individuals who voluntarily registered to undergo a serological test in the metropolitan city of Milan. Consequently, our sample is neither representative of the age distribution, especially due to an under sampling of individuals under 20 years of age, nor of the household composition of the Italian population. Thus, the estimates obtained in this study should be cautiously interpreted. For example, our results may not reflect social behavior adopted in less urbanized areas and individuals who voluntarily seek an IgG test for SARS-CoV-2 antibodies may modify their behavior in response to restrictions in a different manner than the general population. For this reason, instead of relying on absolute numbers, our analysis focuses on investigating the relative differences in the average contact patterns observed across different time periods and at different ages. To reduce potential bias led by the adopted sampling procedure, we also reported the mean number of daily contacts and the age-specific contact matrices as obtained through a bootstrap procedure to adjust our estimates to the age distribution of the population in Milan finding consistent results. In addition, the potential impact of tier restrictions on the number of reported daily contacts was assessed by adopting a regression model, where a variety of potential confounding factors are considered, including age and household composition.

The performed contact study captures only the temporal changes in the overall number of contacts, defined as social interactions either involving a conversation consisting of at least 5 words or a physical contact, and not on their duration. Contact duration may be an important factor associated with the per-contact transmission risk and when strict measures are implemented as the absolute decrease in the overall number of contacts could be partially counterbalanced by an increase of the contact duration with close contacts (e.g., household members). Despite the contribution of contacts occurring outdoor showing a progressive temporal decrease and is highest in the reference period, which coincides with late summer 2020, the current study does not investigate potential seasonal trends and this aspect deserves further investigation.

Additional caveats should be mentioned to correctly interpret the expected change of the SARS-CoV-2 reproduction number under different tiers. Our estimates reflect only the impact of different restriction levels on the transmission when assuming constant epidemiological conditions over time. This means that we did not consider other factors which are known to strongly influence the spread of COVID-19, such as the level of immunity accrued over the course of the pandemic from natural infection or through the rollout of vaccination. The impact of vaccination should be negligible in our analyses, since the vaccine rollout in Italy started on December 27, 2020, prioritizing specific vulnerable groups (e.g., healthcare workers) and less than 5 % of the population in the study area was vaccinated with 1 dose by the end of the study period. Simple compartmental models and the assumption of constant probability of transmission may also be partially inappropriate when strict restrictions on contacts are applied since, under these circumstances, contacts relevant for transmission are likely clustered within specific groups of individuals (e.g., household members).

Moreover, our estimates of the reduction of social contacts under different restriction tiers do not differentiate between changes in the transmission led by the imposed measures and those determined by spontaneous behavioral responses to changes in the perceived risk. Although our analysis does not account for all the complexities of the transmission process in the real world, like the clustering and saturation of contacts, it should be considered as first-order approximation of a more complex dynamics. In fact, the reduction of the reproduction number we estimated using contacts matrices derived for different tiers was consistent with the corresponding variations estimated directly from the time-series of symptomatic cases (Manica et al., 2021).

Our estimates of the contact patterns under different levels of interventions could be used to approximate the expected contribution of different restriction levels in decreasing the transmission of SARS-CoV-2 independently from the epidemiological situation, and they can therefore be instrumental for the control of future COVID-19 epidemics. Moreover, our approach could be generalizable to further monitor changes in social contacts during different epidemic phases or to evaluate alternative measures put in place to control the transmission of different infectious diseases.

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CRediT authorship contribution statement

Filippo Trentini: Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Adriana Manna:** Data curation, Writing – review & editing. **Nicoletta Balbo:** Writing – review & editing. **Valentina Marziano:** Writing – review & editing. **Giorgio Guzzetta:** Writing – review & editing. **Samantha O'Dell:** Data curation, Writing – review & editing. **Allisandra G. Kummer:** Data curation, Writing – review & editing. **Maria Litvinova:** Data curation, Methodology, Writing – review & editing. **Stefano Merler:** Writing – review & editing. **Marco Ajelli:** Conceptualization, Methodology, Writing – review & editing. **Piero Poletti:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Alessia Melegaro:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Competing interests

M.A. has received research funding from Seqirus. The funding is not related to COVID-19 and to this study. The contents of this publication are the sole responsibility of the authors and don't necessarily reflect the views of the funders. All other authors declare no competing interest.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2022.100601.

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