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Complete List of Authors:	Morina, Nexhmedin ; University of Münster, Psychology Kip, Ahlke; University of Münster, Psychology Hoppen, Thole; University of Münster, Psychology Priebe, Stefan; Queen Mary University of London Faculty of Medicine and Dentistry, Unit of Social and Community Psychiatry Meyer, Thomas; University of Münster, Psychology
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A potential impact of social distancing on physical and mental health. A rapid narrative umbrella review of meta-analyses on the link between social isolation and health

Nexhmedin Morina, Ph.D.[1], Ahlke Kip, M.Sc.[1], Thole H. Hoppen, Ph.D.[1], Stefan Priebe, FRCPsych[2], Thomas Meyer, Ph.D.[1]

[1] Institute of Psychology, University of Münster, Münster, Germany

[2] Unit for Social and Community Psychiatry, Queen Mary University of London, London, UK

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* Corresponding Author

Nexhmedin Morina, Ph.D.

Institute of Psychology

University of Münster

Fliednerstr. 21, 48149 Münster, Germany

e-Mail: morina@uni-muenster.de

Abstract

Background: The imperative for social distancing during the coronavirus disease 2019 (COVID-19) pandemic may deteriorate physical and mental health. We aimed at summarizing the strength of evidence in the published literature on the association of social isolation and loneliness with physical and mental health.

Methods: We conducted a systematic search in April 2020 to identify meta-analyses using the Medline, PsycINFO, and Web of Science databases. The search strategy included terms of social isolation, loneliness, living alone, and meta-analysis. Eligible meta-analyses needed to report any sort of association between an indicator of social isolation and any physical or mental health outcome. The findings were summarized in a narrative synthesis.

Results: Twenty-five meta-analyses met our criteria, of which 10 focused on physical health and 15 on mental health outcomes. A total of more than 3 million individuals had participated in the 692 primary studies. The results suggest that social isolation is associated with chronic physical symptoms, frailty, coronary heart disease, malnutrition, hospital readmission, reduced vaccine uptake, early mortality, depression, social anxiety, psychosis, cognitive impairment in later life, and suicidal ideation.

Conclusions: The existing evidence clearly indicates that social isolation is associated with a range of poor physical and mental health outcomes. A potential negative impact on these outcomes needs to be considered in future decisions on social distancing measures.

Keywords: Social isolation, loneliness, physical health, mental health, disease.

Strengths and limitations of this study:

- This rapid umbrella review focuses on a timely and societally relevant issue.
- The systematic literature search was conducted in three major databases from inception up to April 2020 warranting an extensive and up-to-date overview on relevant meta-analyses in the field.
- Quality of included meta-analyses was rated with a standardized measure.
- Different indicators of social isolation were included.
- The utilized method did not allow for a quantitative comparison of associations with health outcomes.

Background

The coronavirus 2019 (COVID-19) pandemic poses a global public health threat. In order to slow the spread of the virus by reducing contact rates, governments around the world have taken unprecedented political decisions that have transformed societies. The exact form and extent of these measures have varied, but they always include some type of social distancing making it impossible for people to maintain their normal social life.

In many countries, the restrictions have already been in place for several weeks or months. Depending on the further course of the pandemic with potential new waves, restrictions might continue for longer periods of time or be re-imposed after periods of loosening or abandoning them. When deciding about imposing, continuing or relaxing measures of social distancing, governments have to consider and balance different risks. Whilst social distancing is likely to reduce the risk of spreading the virus, it might generate other risks. These include potential damages to the economy and also possible negative consequences for the health of the population. For a balanced decision on further social distancing measures, evidence is required on whether the measures are likely to impact on a range of health outcomes.

For many people, social distancing can translate into social isolation, when they are prevented from travelling, physical meetings with friends and social activities, in some cases even from leaving their home other than for essential activities. Social isolation is a wide term without a consistent definition in the literature. Three indicators of social isolation are commonly used in research: low number of social contacts, loneliness and living alone.[1] The number of social contacts is a behavioral measure that can – at least in theory – be objectively quantified. Loneliness is an individual's subjective assessment of the quality and quantity of their

social relationships, reflecting a belief that they have too few or too poor relationships, or both. Living alone describes a basic characteristic of an individual's social situation which can be associated with reduced social relationships, but is not necessarily so. Although these three indicators capture distinct aspects of social isolation, they commonly overlap and are associated with each other.

The extent to which individuals are socially isolated can have a profound impact on both physical and psychological well-being.[2] Social isolation is thought to influence health through behavioral and biological pathways.[3] Several studies demonstrate that social isolation is associated with health-relevant behaviors, such as lack of physical activity, poorer sleep, obsessive behavior, as well as neuroendocrine dysregulation,[3] chronic allostatic load,[4] high blood pressure and poor immune functioning.[2,5,6] Furthermore, the magnitude of the effect of social isolation on mortality may be equivalent to or exceed the impacts of deleterious behaviors such as excessive drinking or obesity.[7]

Social distancing with its inevitable increase of social isolation may therefore have a negative impact on physical and mental health. For weighing up this potential impact in policy decisions, the existing evidence needs to be considered. Against this background, we conducted a systematic umbrella review to synthesize the evidence on the association between social isolation and physical and mental health outcomes. As recommended by the World Health Organization (WHO), we explored relevant meta-analyses by means of a rapid review of evidence.[8]

Methods

The aims and methods of this umbrella review were registered with the PROSPERO database (http://www.crd.york.ac.uk/prospero). To select relevant meta-analyses on

the association between social isolation and physical or mental health outcomes we conducted a systematic search on 6th April 2020 using the databases Medline, PsycINFO, and Web of Science. We conducted multi-field searches (in titles, abstracts, and key concepts) using the following terms: social isolation, loneliness, living alone, and meta-analy*, which we combined using the Boolean operators "or" plus "and". Relevant outcomes included any sort of physical or mental health outcome. We applied no restrictions on age of participants, applied research designs (i.e., cross-sectional, longitudinal), or publication language. We first inspected the title and abstract of all hits and then read full texts of the hits that seemed to meet the aforementioned inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting standards were followed to document the process of systematic review selection. [9]

Coding of trial characteristics

Systematic reviews with a quantitative synthesis of trial results (meta-analysis) were retained. Two reviewers (NM & THH) coded and extracted from each meta-analysis several objectively verifiable characteristics: Authors and year of publication, inclusion criteria, number of included primary studies, number of participants and their composition by age and health conditions, study design, type of social connection (number of social contacts/living alone/loneliness) evaluated, clinical outcome, length of follow-up, number of databases searched, and search areas. Furthermore, we extracted the main findings on the association between number of social contacts/living alone/loneliness and health outcomes (correlation values, odds ratios, or hazard ratios, and the corresponding 95% confidence intervals). With respect to the 95% confidence intervals, both values greater than one (or both values

less than one) represent a significant increase (or decrease) as a function of social isolation.

Quality Assessment

The quality of included systematic meta-analyses was independently assessed by two reviewers (AK & TM) using A Measurement Tool to Assess Systematic Reviews – 2 (AMSTAR-2).[10] Following the tool's guidelines, the raters assigned one of four global quality ratings (i.e., high, moderate, low, or critically low) after consideration of 16 potential critical and non-critical weaknesses. Items addressing the following criteria were considered as critical: Clear research question including definitions of population, intervention, control group, and outcomes (PICO), adequacy of the literature search, and adequate assessment and/or consideration of risk of bias in the primary studies. Typically, high and moderate ratings reflect the presence of one or more non-critical weakness, while low and critically low ratings indicate one or more critical weaknesses. Any discrepancies among the independent raters were discussed until consensus was reached.

Results

Selection and characteristics of included studies

Figure 1 displays a PRISMA[9] flow diagram of the publication selection process. After reading 530 abstracts, 89 full text publications were reviewed. The final review resulted in 25 meta-analyses. Relevant characteristics of these meta-analyses are summarized in Table 1.

Table 1: *Overview of the included meta-analyses*

Publication ↳Results:	Social connections	Clinical outcome	Study design	Age: *M* (*SD*), range, or cut-off	Search: timespan	Range of follow-up	*N* data-bases searched	Quality score
Studies on physical health:								
Besora-Moreno et al., 2020	Living alone	Malnutrition/ malnutrition risk	Cross-sectional	60+	01.2000 - 12.2018	n.a.	2	L
Results:	Living alone		Combined effect			**OR=1.92** (95% CI: 1.73–2.14); *k*=10; *N*=9,042		
Heidari Gorji et al., 2019	Living alone, low number of social contacts, loneliness	Hospital readmission in heart failure patients	Longitudinal	70.87 (8.62)	up to 11.2018	13 months	6	H
Results:	Any type of poor social connection		Combined effect			**OR=1.55** (95% CI: 1.39–1.73); *k*=13; *N*=6,468		
	Living alone or low number of social contacts		Combined effect			**OR=1.52** (95% CI: 1.24–1.86); *k*=6; *N*=3,812		
	Loneliness		Combined effect			**OR=1.63** (95% CI: 1.31–2.01); *k*=7; *N*=2,656		
Holt-Lunstad et al., 2015	Living alone, low number of social contacts, loneliness	Early mortality	Longitudinal	66.00 (n.r.)	01.1980 - 02.2014	7.1 years	5	L
Results:	Living alone		Unadjusted studies			**OR=1.51** (95% CI: 1.32–1.74); *k*=20; *N*=n.r.		
	Living alone		Studies with multiple covariates			**OR=1.32** (95% CI: 1.14–1.53); *k*=25; *N*=n.r.		
	Low number of social contacts		Unadjusted studies			**OR=1.83** (95% CI: 1.27–2.63); *k*=3; *N*=n.r.		
	Low number of social contacts		Studies with multiple covariates			**OR=1.29** (95% CI: 1.06–1.56); *k*=14; *N*=n.r.		
	Loneliness		Unadjusted studies			**OR=1.49** (95% CI: 1.22–1.84); *k*=8; *N*=n.r.		
	Loneliness		Studies with multiple covariates			**OR=1.26** (95% CI: 1.04–1.53); *k*=13; *N*=n.r.		
Jain et al., 2017	Living alone	Reduced vaccine uptake in older adults	Cross-sectional [a]	60+	up to 02.2016	n.r.	2	M
Results:	Living alone		Seasonal influenza vaccine			**OR=1.39** (95% CI: 1.16–1.68); *k*=9; *N*=40,551		
	Living alone		Pneumococcal vaccine			**OR=1.71** (95% CI: 1.20–2.46); *k*=1; *N*=1,702		

Kojima et al., 2020	Living alone	Frailty in older adults	Cross-sectional & longitudinal	60+	2000 - 02.2019	n.r.	1	L
Results:	Living alone		Cross-sectional studies			**OR=1.28** (95% CI: 1.13–1.45); *k*=44; *N*=113,374		
			Sub-analysis: only men			**OR=1.71** (95% CI: 1.49–1.96); *k*=20; *N*=n.r.		
			Sub-analysis: only women			OR=1.00 (95% CI: 0.83–1.20); *k*=22; *N*=n.r.		
			Sub-analysis: >=60, <70 years old			**OR=1.67** (95% CI: 1.51–1.86); *k*=4; *N*=n.r.		
			Sub-analysis: >=80 years old			OR=0.96 (95% CI: 0.69–1.31); *k*=6; *N*=n.r.		
	Living alone		Longitudinal studies			OR=0.88 (95% CI: 0.76–1.03); *k*=6; *N*=38,549		
Maes et al., 2017	Loneliness	Chronic physical conditions in children/adolescents	Cross-sectional [a]	children < 12 and adolescents < 21	1987 – 06.2016	n.r.	4	L
Results:	Loneliness		Combined effect (excl. 3 outliers)			**g=0.17** (95% CI: 0.03–0.30); *k*=40; *N*=3,981		
			Sub-analysis: control group studies			**g=0.13** (95% CI: 0.01–0.26); *k*=23; *N*=2,995		
			Sub-analysis: hearing/visual problems			**g=0.43** (n.r.); *k*=8; *N*=770		
Rico-Uribe et al., 2018	Loneliness	Early mortality	Longitudinal	Mainly 50+	up to 06.2016	n.r.	4	H
Results:	Loneliness		Combined effect			**HR=1.22** (95% CI: 1.10–1.35); *k*=31; *N*=77,220		
			Sub-analysis: only men			**HR=1.44** (95% CI: 1.19-1.76); *k*=7; *N*=5,815		
			Sub-analysis: only women			**HR=1.26** (95% CI: 1.07-1.48); *k*=7; *N*=10,248		
Smith et al, 2020	Low number of social contacts, loneliness	Inflammation markers	Cross-sectional [a]	16+	up to 07.2019	n.r.	5	H
Results:	Low number of social contacts		C-reactive protein: unadjusted studies			***r*=.186** (95% CI: .063–.303); *k*=7; *N*=41,126		
			C-reactive protein: adjusted studies			*r*=.021 (95% CI: .051–.092); *k*=11; *N*=41,911		
			Fibrinogen: unadjusted studies			***r*=.103** (95% CI: .043–.163); *k*=6; *N*=15,421		
			Fibrinogen: adjusted studies			***r*=.039** (95% CI: .011–.067); *k*=6; *N*=22,161		
			Interleukin-6: unadjusted studies			*r*=.267 (95% CI: -.341–.718); *k*=4; *N*=12,291		
			Interleukin-6: adjusted studies			*r*=-.003 (95% CI: -.148–.141); *k*=6; *N*=14,243		
	Loneliness		C-reactive protein: unadjusted studies			*r*=.047 (95% CI: -.003–.098); *k*=8; *N*=17,835		
			C-reactive protein: adjusted studies			*r*=.023 (95% CI: -.018–.065); *k*=6; *N*=19,292		
			Fibrinogen: unadjusted studies			*r*=.006 (95% CI: -.057–.070); *k*=3; *N*=1,806		

			Fibrinogen: adjusted studies			*r*=.037 (95% CI: -.015–.089); *k*=4; *N*=7,672		
			Interleukin-6: unadjusted studies			*r*=.082 (95% CI: -.001–.163); *k*=4; *N*=4,219		
			Interleukin-6: adjusted studies			***r*=.070** (95% CI: .015–.124); *k*=2; *N*=1,451		
Steptoe & Kivimäki, 2013	Social isolation, loneliness	Cardiovascular disease	Longitudinal	n.r.	up to 2011	n.r.	n.r.	CL
Results:	Low number of social contacts or loneliness		Combined effect			**RR=1.51** (95% CI: 1.21–1.88); *k*=7; *N*=n.r.		
Valtorta et al., 2016	Social isolation, loneliness	Coronary heart disease and stroke	Longitudinal	18+	up to 05.2015	3 to 21 years	16	H
Results:	Low number of social contacts or loneliness		Coronary heart disease			**RR=1.29** (95% CI: 1.04–1.59); *k*=11; *N*=n.r.		
	Low number of social contacts		Stroke incidence			**RR=1.32** (95% CI: 1.04–1.68); *k*=9; *N*=n.r.		
Studies on mental health:								
Chang et al., 2017	Living alone, loneliness	Late-life suicidal ideation	Cross-sectional [a]	50+	01.2000 - 11.2016	n.r.	7	L
Results:	Living alone		Combined effect			**OR=1.38** (95% CI: 1.19–1.61); *k*=8; *N*=102,401		
	Loneliness		Combined effect			**OR=2.24** (95% CI: 1.73–2.90); *k*=3; *N*=58,482		
Chatterjee et al., 2018	Low number of social contacts, loneliness	Depression in civilians after 9/11	Longitudinal	43.78 (n.r.)	09.2001 - 07.2016	n.r.	3	L
Results:	Low number of social contacts or loneliness		Combined effect			**OR=1.68** (99.5% CI:1.13–2.49); k=4; N=27,395		
Chau et al., 2019	Loneliness	Psychosis	Cross-sectional [a]	Adults (mainly)	up 10.2018	n.r.	5	M
Results:	Loneliness		Positive symptoms			***r*=.302** (95% CI: .243–.359); *k*=30; *N*=17,832		
			Sub-analysis: clinical populations			***r*=.149** (95% CI: .057–.238); *k*=14; *N*=n.r.		
			Sub-analysis: non-clinical populations			***r*=.389** (95% CI: .232–.526); *k*=5; *N*=n.r.		
			Sub-analysis: mixed populations			***r*=.366** (95% CI: .308–.422); *k*=12; *N*=n.r.		
			Sub-analysis: Paranoia			***r*=.448** (95% CI: .371–.519); *k*=7; *N*= n.r.		
			Sub-analysis: Hallucinations			***r*=.201** (95% CI: .101–.297); *k*=10; *N*= n.r.		
	Loneliness		Negative psychotic symptoms			***r*=.347** (95% CI: .239–.446); *k*=15; *N*=5,567		
			Sub-analysis: clinical populations			***r*=.127** (95% CI: .029–.223); *k*=9; *N*=n.r.		
			Sub-analysis: non-clinical populations			***r*=.479** (95% CI: .351–.589); *k*=4; *N*=n.r.		
			Sub-analysis: mixed populations			***r*=.547** (95% CI: .464–.620); *k*=2; *N*=n.r.		

Choi & Smith, 2013	Low number of social contacts	Adolescents' smoking behaviors	Cross-sectional	< 19	n.r.	n.a.	3	CL
Results:	Low number of social contacts		Network position: isolate vs. member			**OR=1.55** (95% CI: 1.32–1.81); *k*=8; *N*=5,067		
			Network position: isolated vs. liaison			**OR=1.49** (95% CI: 1.07–2.07); *k*=8; *N*=5,067		
Erzen & Çikrikci, 2018	Loneliness	Depression	Cross-sectional [a]	Adults	up to 01.2018	n.r.	2	CL
Results:	Loneliness		Combined effect			***r*=.50** (95% CI: .44–.55); *k*=88; *N*=40,068		
			Sub-analysis: clinical populations			***r*=.54** (95% CI: .38–.67); *k*=10; *N*=n.r.		
			Sub-analysis: other populations			***r*=.44** (95% CI: .16–.66); *k*=12; *N*=n.r.		
Evans et al., 2018	Low number of social contacts	Cognitive functioning	Longitudinal	50+	up to 01.2018	2-24 years	4	M
Results:	Low number of social contacts		Combined effect			***r*=.054** (95% CI: .043–.065); *k*=51; *N*=102,035		
			Sub-analysis: global measures			***r*=.061** (95% CI: .044–.079); *k*=43; *N*=74,933		
			Sub-analysis: memory			***r*=.050** (95% CI: .028–.072); *k*=13; *N*=35,230		
			Sub-analysis: executive functioning			***r*=.031** (95% CI: .015–.047); *k*=7; *N*=30,528		
Kuiper et al., 2015	Low number of social contacts, loneliness	Risk of dementia	Longitudinal	60+	up to 07.2012	2 to 15 years	3	M
Results:	Low number of social contacts		Low social network size			RR=1.17 (95% CI: 0.92–1.48); *k*=5; *N*=7,749		
	Low number of social contacts		Low level of participation			**RR=1.41** (95% CI: 1.13–1.75); *k*=6; *N*=7,687		
	Low number of social contacts		Low frequency of contacts			**RR=1.57** (95% CI: 1.32–1.85); *k*=8; *N*=15,762		
	Loneliness		Feeling lonely			**RR=1.58** (95% CI: 1.19–2.09); *k*=3; *N*=3,252		
	Loneliness		Low satisfaction with social network			RR=1.25 (95% CI: 0.96–1.62); *k*=4; *N*=6,207		
Lara et al., 2019	Loneliness	Dementia & mild cognitive impairment	Longitudinal	50+	up to 11.2018	n.r.	6	H
Results:	Loneliness		Combined effect			**RR=1.26** (95% CI: 1.14–1.40); *k*=8; *N*=33,555		
Maes et al., 2019	Loneliness	Social anxiety in children/adolescents	Cross-sectional & longitudinal	15.59 (4.27)	1981 – 06.2016	1.25 to 72 months	4	CL
Results:	Loneliness		Cross-sectional effects			***r*=.46** (95% CI: .43–.48); *k*=98; *N*=41,776		
	Loneliness		Longitudinal/cross-lagged effects			***r*=.12** (95% CI: .04–.21); *k*=10; *N*=3,995		
Mahon et al., 2006	Loneliness	Depression & social anxiety in adolescence	Cross-sectional [a]	Adolescents (11 to 23)	1980 - 2004	n.r.	4	CL

Results:	Loneliness		Depression			***r*=.61** (n.r.); *k*=30; *N*=17,691		
			Sub-analysis: outliers removed			***r*=.55** (n.r.); *k*=18; *N*=6,058		
	Loneliness		Anxiety			***r*=.41** (n.r.); *k*=12; *N*=3,853		
			Sub-analysis: outliers removed			***r*=.35** (n.r.); *k*=10; *N*=2,705		
Michalska da Rocha et al., 2018	Loneliness	Psychosis	Cross-sectional [a]	Adults	up to 02.2016	n.r.	4	H
Results:	Loneliness		Combined effect			***r*=.32** (95% CI: 0.20–0.44); *k*=13; *N*=15,647		
Penninkilampi et al., 2018	Living alone, Low number of social contacts, loneliness	Risk of dementia	Longitudinal & case-control	60+	01.2012 – 05.2017	5.9 years	8	L
Results:	Any type of poor social connection		Combined effect			**RR=1.41** (95% CI: 1.21–1.65); *k*=15; *N*=2,330,163		
	Low number of social contacts		Combined effect			**RR=1.59** (95% CI: 1.31–1.93); *k*=6; *N*=25,373		
	Living alone		Combined effect			**RR=1.41** (95% CI: 1.07–1.84); *k*=4; *N*=5,401		
	Loneliness		Combined effect			RR=1.38 (95% CI: 0.98–1.94); *k*=4; *N*=4,698		
Teo et al., 2013	Living alone	Social anxiety disorder	Cross-sectional [a]	Adults (mainly)	01.1980 - 02.2011	n.r.	4	M
Results:	Living alone		Combined effect			**OR=1.73** (95% CI: 1.34–2.24); *k*=4; *N*=12,831		
			Sub-analysis: large survey studies			**OR=1.70** (95% CI: 1.38–2.10); *k*=3; *N*=12,773		
Xiu-Ying et al., 2012	Living alone	Late life depression	Cross-sectional & longitudinal	55+	1966 - 08.2007	n.r.	3	CL
Results:	Living alone		Cross-sectional effects			**OR=1.44** (95% CI: 1.04–1.99); *k*=16; *N*=34,090		
			Sub-analysis: vs. living with family			**OR=2.59** (95% CI: 1.60–4.20); *k*=5; *N*=12,537		
	Living alone		Longitudinal/cross-lagged effects			RR=1.27 (95% CI: 0.89–1.80); *k*=4; *N*=1,345		
Yuan et al., 2019	Living alone	Post-acute coronary syndrome depression	Longitudinal & case-control	19+	01.1996 - 03.2018	n.r.	4	L
Results:	Living alone		Combined effect			**OR=1.17** (95% CI: 1.12–1.22); *k*=11; *N*=n.r.		

Note: For each result, we specify the type of social connection, the focus of the (sub-)analysis, followed by the reported effect size (in brackets: confidence intervals), as well as included numbers of independent studies and participants. Effect sizes printed in boldface are statistically significant at alpha = 0.05. Abbreviations: n.a.: not applicable; n.r.: not reported; H: High; M: Moderate; L: Low; CL: Critically low.

[a] These studies included different study designs and extracted cross-sectional data or aggregated longitudinal and cross-sectional data.

All publications were journal articles in English. Ten meta-analyses reported associations of number of social contacts, living alone, and loneliness with physical health outcomes, and 15 with mental health outcomes. Different indicators of social isolation were measured in the included studies. We considered as indicators a *low number of social contacts* defined as an objectively quantifiable variable of one's social contacts irrespective of its perceived quality; *loneliness* representing the subjective emotional appraisal of the extent and quality of social relationships; and *living alone* as an objective characteristic of the living situation. The meta-analyses differed with respect to whether they kept these three measures of social isolation separate of whether they combined them (see Tab. 1).

Figure 1 & Table 1

A total of 276 primary studies were included in the 10 meta-analyses on physical health. The reported results in Table 1 were based on sample sizes ranging from 1,451[11] to 113,374[12] participants, with three meta-analyses not reporting on the sample size. Four meta-analyses were based on longitudinal studies only, one on cross-sectional studies only, and the remaining five on a combination of both cross-sectional and longitudinal studies. Only one of these studies was conducted with children and adolescents.[13] The meta-analyses revealed that there is a significant association between social isolation and the following health problems: chronic physical complaints in children and adolescents,[13] cardiovascular disease,[14] coronary heart disease and stroke,[15] and frailty in older male (but not female) adults.[12] Additionally, social isolation was associated with early mortality,[7,16] malnutrition,[17] hospital readmission in heart failure patients,[18] and vaccine uptake amongst older adults.[19] One meta-analysis[11] reported mostly non-significant results on a positive

association between social isolation and inflammation (acute-phase C-reactive protein and fibrinogen).

The 15 meta-analyses on mental health were based on a total of 416 primary studies. The reported results are based on sample sizes ranging from 1,345[20] to 2,330,163[21] participants, with one meta-analysis failing to report on the sample size. Four of the 15 meta-analyses provided longitudinal data only, one provided cross-sectional data only, and the remaining ten meta-analyses reported on both cross-sectional and longitudinal studies. Three meta-analyses focused on studies with children and adolescents.[22-24] The included meta-analyses reported a positive association between social isolation and late-life suicidal ideation,[25] depression in adults,[26,27] late life depression, [20] psychosis,[22,28,29] smoking behavior in adolescents,[23] dementia and cognitive impairment in later life,[30-32,21] depression and social anxiety in childhood and adolescence,[22,24] social anxiety disorder in adults,[33] and post-acute coronary syndrome depression.[34] See Table 1 for detailed information.

Study quality

The Intraclass Correlation Coefficient (ICC) of the global quality ratings among the two raters was .83, 95% CI = .62 – .93, indicating good inter-rater reliability. Study quality was very heterogeneous among meta-analyses both on physical and mental health (see Tab. 1). With respect to the meta-analyses on physical health, the global rating was high in 40%, medium in 10%, low in 40%, critically low in 10% of the meta-analyses. In the 15 meta-analyses on mental health, study quality was rated as high in 13%, medium in 27%, low in 27%, and critically low in 33% of the meta-analyses. Among the AMSTAR-2 criteria, inadequate assessment of risk of bias and/or lack of consideration of risk of bias represented the most frequent critical weaknesses of included meta-analyses.

Discussion

The review clearly demonstrates that social isolation is associated with poorer health. This applies to a range of physical and mental health outcomes and has been found in different populations and contexts. The evidence is substantial for physical health outcome and even more extensive for mental health outcomes. More specifically, social isolation is linked with chronic physical symptoms, frailty, coronary heart disease, stroke, early mortality, malnutrition, hospital readmission in heart failure patients, and vaccine uptake. With respect to mental health, social isolation is linked with depression in young and adult populations, social anxiety, psychosis, dementia and cognitive impairment in later life, and late-life suicidal ideation.

Strengths and limitations

This is, to our knowledge, the first review to synthesize the existing evidence that has been reported in meta-analyses on the link between social isolation and physical and mental health outcomes. The findings reflect a reasonable number of meta-analyses which in total included 692 studies. Thus, the overall conclusions of this umbrella review are based on an extensive body of empirical evidence.

However, the review also has several limitations. Firstly, we considered different indicators of social isolation, and our method did not allow us to identify whether one indicator is more relevant than another. Secondly, half of the included meta-analyses for both physical and mental health outcomes had an overall quality rated on AMSTAR-2 as low or critically low, with inadequate consideration of risk of bias being the most frequent critical flaw. Thirdly, the quality of the primary research studies that went into the included meta-analyses also varied and their different

methodological shortcomings cannot be adequately considered in this review. Finally, the review included a wide range of health outcomes and did not quantify the strength of the associations for different outcomes.

Implications

The review leaves little doubt that social isolation is linked with poorer physical and mental health. However, the findings are all based on observational studies and do not provide evidence on the causal direction of the association. Poor physical and mental health can lead to social isolation, and social isolation can lead to poorer health. For establishing a causal relationship experimental studies are required, which were not the subject of this review. Some evidence from randomized controlled trials, however, suggests that expanding the social connections of individuals, e.g., through befriending programs, may indeed improve different health outcomes.[35] For most of the considered outcomes, a causal effect of social isolation is plausible and likely to explain at least part of the identified associations. The casual direction is definite in case of the greater risk of isolated people to die early.[7] For an explanation of the damaging effect of social isolation on health outcomes, one may refer to different theoretical models. Theorists from different perspectives have postulated that the impact of social isolation on health is mediated by impairments in social capital,[36] social control,[37] social identification,[38] and social support.[39]

All the included studies assessed social isolation as it occurs in a normal societal context. Social distancing as part of measures to limit the spread of COVID-19 is different from the situations considered in the research synthesized in this review. Firstly, for the vast majority of the population, the required social distancing leads to a much more pronounced social isolation than what they have experienced

before. Secondly, social distancing is externally imposed and not due to individual life style decisions, lack of material means, poor social skills or other barriers to socialize. And thirdly, social distancing is requested from people in an overall context of uncertainty that comes with further stressors, health risks, and often a reduced accessibility of health care.

It is important to note that social distancing is a broad umbrella term that incorporates a wide range of potential measures, with highly divergent implications for social routines. It can include a full lock down and curfew, specific guidelines for meetings and gatherings of people, physical distancing in public, and a recommended or mandatory wearing of face masks. The type, degree, and duration of social distancing measures have been variable across countries and will affect how isolated different groups in the population become.

One can only speculate as to whether and, if so, to what extent the increased social isolation resulting from social distancing measures in the current situation will have an even greater impact on health outcomes than has been suggested in this review. Arguably, an even greater impact can be expected for certain risk groups, such as older people who are more threatened by COVID-19 and socially disadvantaged groups who often face even more economic adversity than before the pandemic. Further research is required to identify which populations are at particular risk to suffer health problems as a result of social distancing and to explore whether the resulting social isolation may – at least to some extent and in some people – be compensated through positive effects of the pandemic, such as strengthened local communities and increased options for online social activities.[40]

Conclusions

In governmental decisions about future social distancing measures, a potential negative impact of the resulting social isolation on the health of the population needs to be considered. This review suggests that this can affect both physical and mental health outcomes and include an excess mortality. To what extent the presumed impact of social distancing on health outcomes can be balanced with its benefits in curbing the impact of COVID-19 is ultimately a governmental decision based on values as much as on evidence.

Figure Captions: Fig.1. Flow diagram of study selection process.

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Authors' Contributions: NM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
NM designed the search strategy with input from AK and TM. NM and AK carried out the literature searches and screening. NM, THH, and TM carried out the data extraction. AK and TM assessed the quality of the included meta-analyses. NM and SP wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

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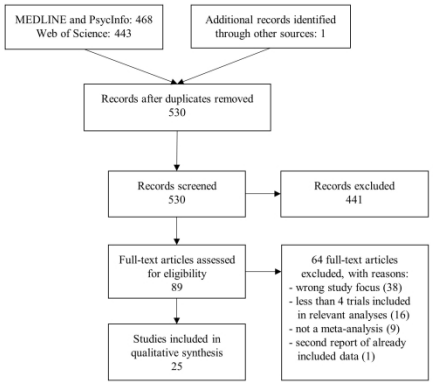

Fig. 1. Flow diagram of study selection process

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A potential impact of physical distancing on physical and mental health. A rapid narrative umbrella review of meta-analyses on the link between social isolation and health

Nexhmedin Morina, Ph.D.[1], Ahlke Kip, M.Sc.[1], Thole H. Hoppen, Ph.D.[1], Stefan Priebe, FRCPsych[2], Thomas Meyer, Ph.D.[1]

[1] Institute of Psychology, University of Münster, Münster, Germany

[2] Unit for Social and Community Psychiatry, Queen Mary University of London, London, UK

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* Corresponding Author

Nexhmedin Morina, Ph.D.

Institute of Psychology

University of Münster

Fliednerstr. 21, 48149 Münster, Germany

e-Mail: morina@uni-muenster.de

Abstract

Background: The imperative for physical distancing during the coronavirus disease 2019 (COVID-19) pandemic may deteriorate physical and mental health. We aimed at summarizing the strength of evidence in the published literature on the association of social isolation and loneliness with physical and mental health.

Methods: We conducted a systematic search in April 2020 to identify meta-analyses using the Medline, PsycINFO, and Web of Science databases. The search strategy included terms of social isolation, loneliness, living alone, and meta-analysis. Eligible meta-analyses needed to report any sort of association between an indicator of social isolation and any physical or mental health outcome. The findings were summarized in a narrative synthesis.

Results: Twenty-five meta-analyses met our criteria, of which 10 focused on physical health and 15 on mental health outcomes. A total of more than 3 million individuals had participated in the 692 primary studies. The results suggest that social isolation is associated with chronic physical symptoms, frailty, coronary heart disease, malnutrition, hospital readmission, reduced vaccine uptake, early mortality, depression, social anxiety, psychosis, cognitive impairment in later life, and suicidal ideation.

Conclusions: The existing evidence clearly indicates that social isolation is associated with a range of poor physical and mental health outcomes. A potential negative impact on these outcomes needs to be considered in future decisions on physical distancing measures.

Keywords: Social isolation, loneliness, physical health, mental health, disease.

Strengths and limitations of this study:

- This rapid umbrella review focuses on a timely and societally relevant issue.
- The systematic literature search was conducted in three major databases from inception up to April 2020 warranting an extensive and up-to-date overview on relevant meta-analyses in the field.
- Quality of included meta-analyses was rated with a standardized measure.
- Different indicators of social isolation were included.
- The utilized method did not allow for a quantitative comparison of associations with health outcomes.

Background

The coronavirus 2019 (COVID-19) pandemic poses a global public health threat. In order to slow the spread of the virus by reducing contact rates, governments around the world have taken unprecedented political decisions that have transformed societies. The exact form and extent of these measures have varied, but they always include some type of physical distancing (mostly referred to as social distancing) making it impossible for people to maintain their normal social life.

In many countries, the restrictions have already been in place for several months. Depending on the further course of the pandemic with potential new waves, restrictions might continue for longer periods of time or be re-imposed after periods of loosening or abandoning them. When deciding about imposing, continuing or relaxing measures of physical distancing, governments have to consider and balance different risks. Whilst physical distancing is likely to reduce the risk of spreading the virus, it might generate other risks. These include potential damages to the economy and also possible negative consequences for the health of the population. For a balanced decision on further physical distancing measures, evidence is required on whether the measures are likely to impact on a range of health outcomes.

A recent general population survey revealed that physical distancing can increase social isolation and loneliness.[1] This may happen when people are prevented from travelling, physical meetings with significant others, and in some cases even from leaving their home other than for essential activities. Of note, some individuals can be physically isolated and not feel lonely and others can feel lonely even if they are not isolated. Furthermore, many individuals are able to remain socially connected by means of remote communication while physically isolated. Accordingly, we should not assume that physical distancing inevitably leads to social isolation and

loneliness. However, physical distancing is likely to have a disproportionate effect on those most vulnerable, in particular older adults, individuals in need of intensive physical or mental health care, and individuals with limited access to technology who lack the means of engaging in creative forms of contact with loved ones. Older patients, for example, may lose access to important parts of their usual routine (e.g., day care programs or informal gatherings with significant others). Similarly, caregivers residing with patients need also to physically isolate themselves due to the ramifications of quarantines.

Social isolation is a broad term without a consistent definition in the literature. Three indicators of social isolation (also referred to as social connections) are commonly used in research: few social network ties, living alone, and loneliness.[2-4] Social network ties is a behavioral measure that can – at least in theory – be objectively quantified. Living alone describes a basic characteristic of an individual's social situation which can be associated with reduced social relationships, but is not necessarily so.[5] Loneliness, on the other hand, is an individual's subjective assessment of the quality and quantity of their social relationships, reflecting a belief that they have too few or too poor relationships, or both. Accordingly, social network ties and living alone represent structural indicators, whereas loneliness represents a quality measure of social connections.[4,5]

Although these three indicators capture distinct aspects of social isolation, they commonly overlap and are associated with each other. Literature suggests that many individuals are socially isolated or lonely or both and that social isolation and loneliness may occur unequally across age groups. For example, Hawkley and colleagues[6] reported that loneliness decreased with age through the early 70s and then increased again. Several studies indicate that at least a fifth of adults report frequent

loneliness,[7,8] and that more than 40 percent of adults aged 60 and older report feeling lonely.[9]

The extent to which individuals are socially isolated can have a profound impact on both physical and psychological well-being.[5] Social isolation is thought to influence health through behavioral and biological pathways.[10] Several studies demonstrate that social isolation is associated with health-relevant behaviors, such as lack of physical activity, poorer sleep, obsessive behavior, as well as neuroendocrine dysregulation,[10] chronic allostatic load,[11] high blood pressure and poor immune functioning.[5,12,13] Furthermore, the magnitude of the effect of social isolation on mortality may be equivalent to or exceed the impacts of deleterious behaviors such as excessive drinking or obesity.[3]

Physical distancing may increase social isolation therefore have a negative impact on physical and mental health. For weighing up this potential impact in policy decisions, the existing evidence needs to be considered. Against this background, we conducted a systematic umbrella review to synthesize the evidence on the association between social isolation and physical and mental health outcomes. As recommended by the World Health Organization (WHO), we explored relevant meta-analyses by means of a rapid review of evidence.[14]

Methods

The aims and methods of this umbrella review were registered with the PROSPERO database (http://www.crd.york.ac.uk/prospero). To select relevant meta-analyses on the association between social isolation and physical or mental health outcomes we conducted a systematic search on 6th April 2020 using the databases Medline, PsycINFO, and Web of Science. We conducted multi-field searches (in titles,

abstracts, and key concepts) using the following terms: social isolation, loneliness, living alone, and meta-analy*, which we combined using the Boolean operators “or” plus “and”. The full search string for Medline and PsycINFO was "((TI Loneliness OR AB loneliness OR SU Loneliness) OR (TI social isolation OR AB social isolation OR SU social isolation) OR (TI living alone OR AB living alone OR SU living alone)) AND (TI meta-analy* OR AB meta-analy* OR SU meta-analy*)". Relevant outcomes included any sort of physical or mental health outcome. We applied no restrictions on age of participants, applied research designs (i.e., cross-sectional, longitudinal), or publication language. Furthermore, we did not apply any limits. We first inspected the title and abstract of all hits and then read full texts of the hits that seemed to meet the aforementioned inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting standards were followed to document the process of systematic review selection. [15]

Coding of trial characteristics

Systematic reviews with a quantitative synthesis of trial results (meta-analysis) were retained. Two reviewers (NM & THH) coded and extracted from each meta-analysis several objectively verifiable characteristics: Authors and year of publication, inclusion criteria, number of included primary studies, number of participants and their composition by age and health conditions, study design, type of social connection (social network ties/living alone/loneliness) evaluated, clinical outcome, length of follow-up, number of databases searched, and search areas. Furthermore, we extracted the main findings on the association between social network ties/living alone/loneliness and health outcomes (correlation values, odds ratios, or hazard ratios, and the corresponding 95% confidence intervals). With respect to the 95% confidence

intervals, both values greater than one (or both values less than one) represent a significant increase (or decrease) as a function of social isolation.

Quality Assessment

The quality of included systematic meta-analyses was independently assessed by two reviewers (AK & TM) using A Measurement Tool to Assess Systematic Reviews – 2 (AMSTAR-2).[16] Following the tool's guidelines, the raters assigned one of four global quality ratings (i.e., high, moderate, low, or critically low) after consideration of 16 potential critical and non-critical weaknesses. Items addressing the following criteria were considered as critical: Clear research question including definitions of population, intervention, control group, and outcomes (PICO), adequacy of the literature search, and adequate assessment and/or consideration of risk of bias in the primary studies. Typically, high and moderate ratings reflect the presence of one or more non-critical weakness, while low and critically low ratings indicate one or more critical weaknesses. Any discrepancies among the independent raters were discussed until consensus was reached.

Results

Selection and characteristics of included studies

Figure 1 displays a PRISMA[15] flow diagram of the publication selection process. After reading 530 abstracts, 89 full text publications were reviewed. The final review resulted in 25 meta-analyses. Relevant characteristics of these meta-analyses are summarized in Table 1.

Table 1: *Overview of the included meta-analyses*

Publication ↳Results:	Social connections	Clinical outcome	Study design	Age: *M* (*SD*), range, or cut-off	Literature search: timespan	Range of follow-up	*N* data-bases searched	Quality score
Studies on physical health:								
Besora-Moreno et al., 2020	Living alone	Malnutrition/ malnutrition risk	Cross-sectional	60+	01.2000 - 12.2018	n.a.	2	L
Results:	Living alone		Combined effect			**OR=1.92** (95% CI: 1.73–2.14); *k*=10; *N*=9,042		
Heidari Gorji et al., 2019	Living alone, few social network ties, loneliness	Hospital readmission in heart failure patients	Longitudinal	70.87 (8.62)	up to 11.2018	13 months	6	H
Results:	Any type of poor social connection		Combined effect			**OR=1.55** (95% CI: 1.39–1.73); *k*=13; *N*=6,468		
	Living alone or few social network ties		Combined effect			**OR=1.52** (95% CI: 1.24–1.86); *k*=6; *N*=3,812		
	Loneliness		Combined effect			**OR=1.63** (95% CI: 1.31–2.01); *k*=7; *N*=2,656		
Holt-Lunstad et al., 2015	Living alone, few social network ties, loneliness	Early mortality	Longitudinal	66.00 (n.r.)	01.1980 - 02.2014	7.1 years	5	L
Results:	Living alone		Unadjusted studies			**OR=1.51** (95% CI: 1.32–1.74); *k*=20; *N*=n.r.		
	Living alone		Studies with multiple covariates			**OR=1.32** (95% CI: 1.14–1.53); *k*=25; *N*=n.r.		
	Few social network ties		Unadjusted studies			**OR=1.83** (95% CI: 1.27–2.63); *k*=3; *N*=n.r.		
	Few social network ties		Studies with multiple covariates			**OR=1.29** (95% CI: 1.06–1.56); *k*=14; *N*=n.r.		
	Loneliness		Unadjusted studies			**OR=1.49** (95% CI: 1.22–1.84); *k*=8; *N*=n.r.		
	Loneliness		Studies with multiple covariates			**OR=1.26** (95% CI: 1.04–1.53); *k*=13; *N*=n.r.		
Jain et al., 2017	Living alone	Reduced vaccine uptake in older adults	Cross-sectional[a,b]	60+	up to 02.2016	n.r.	2	M
Results:	Living alone		Seasonal influenza vaccine			**OR=1.39** (95% CI: 1.16–1.68); *k*=9; *N*=40,551		
	Living alone		Pneumococcal vaccine			**OR=1.71** (95% CI: 1.20–2.46); *k*=1; *N*=1,702		

Kojima et al., 2020	Living alone	Frailty in older adults	Cross-sectional[b] & longitudinal[b]	60+	2000 - 02.2019	n.r.	1	L
Results:	Living alone		Cross-sectional studies			**OR=1.28** (95% CI: 1.13–1.45); *k*=44; *N*=113,374		
			Sub-analysis: only men			**OR=1.71** (95% CI: 1.49–1.96); *k*=20; *N*=n.r.		
			Sub-analysis: only women			OR=1.00 (95% CI: 0.83–1.20); *k*=22; *N*=n.r.		
			Sub-analysis: >=60, <70 years old			**OR=1.67** (95% CI: 1.51–1.86); *k*=4; *N*=n.r.		
			Sub-analysis: >=80 years old			OR=0.96 (95% CI: 0.69–1.31); *k*=6; *N*=n.r.		
	Living alone		Longitudinal studies			OR=0.88 (95% CI: 0.76–1.03); *k*=6; *N*=38,549		
Maes et al., 2017	Loneliness	Chronic physical conditions in children/adolescents	Cross-sectional[a]	children < 12 and adolescents < 21	1987 – 06.2016	n.r.	4	L
Results:	Loneliness		Combined effect (excl. 3 outliers)			**g=0.17** (95% CI: 0.03–0.30); *k*=40; *N*=3,981		
			Sub-analysis: control group studies			**g=0.13** (95% CI: 0.01–0.26); *k*=23; *N*=2,995		
			Sub-analysis: hearing/visual problems			**g=0.43** (n.r.); *k*=8; *N*=770		
Rico-Uribe et al., 2018	Loneliness	Early mortality	Longitudinal[b]	Mainly 50+	up to 06.2016	n.r.	4	H
Results:	Loneliness		Combined effect			**HR=1.22** (95% CI: 1.10–1.35); *k*=31; *N*=77,220		
			Sub-analysis: only men			**HR=1.44** (95% CI: 1.19-1.76); *k*=7; *N*=5,815		
			Sub-analysis: only women			**HR=1.26** (95% CI: 1.07-1.48); *k*=7; *N*=10,248		
Smith et al, 2020	Few social network ties, loneliness	Inflammation markers	Cross-sectional[a]	16+	up to 07.2019	n.r.	5	H
Results:	Few social network ties		C-reactive protein: unadjusted studies			***r*=.186** (95% CI: .063–.303); *k*=7; *N*=41,126		
			C-reactive protein: adjusted studies			*r*=.021 (95% CI: .051–.092); *k*=11; *N*=41,911		
			Fibrinogen: unadjusted studies			***r*=.103** (95% CI: .043–.163); *k*=6; *N*=15,421		
			Fibrinogen: adjusted studies			***r*=.039** (95% CI: .011–.067); *k*=6; *N*=22,161		
			Interleukin-6: unadjusted studies			*r*=.267 (95% CI: -.341–.718); *k*=4; *N*=12,291		
			Interleukin-6: adjusted studies			*r*=-.003 (95% CI: -.148–.141); *k*=6; *N*=14,243		
	Loneliness		C-reactive protein: unadjusted studies			*r*=.047 (95% CI: -.003–.098); *k*=8; *N*=17,835		
			C-reactive protein: adjusted studies			*r*=.023 (95% CI: -.018–.065); *k*=6; *N*=19,292		
			Fibrinogen: unadjusted studies			*r*=.006 (95% CI: -.057–.070); *k*=3; *N*=1,806		

			Fibrinogen: adjusted studies			*r*=.037 (95% CI: -.015–.089); *k*=4; *N*=7,672		
			Interleukin-6: unadjusted studies			*r*=.082 (95% CI: -.001–.163); *k*=4; *N*=4,219		
			Interleukin-6: adjusted studies			***r*=.070** (95% CI: .015–.124); *k*=2; *N*=1,451		
Steptoe & Kivimäki, 2013	Few social network ties, loneliness	Cardiovascular disease	Longitudinal[b]	n.r.	up to 2011	n.r.	n.r.	CL
Results:	Few social network ties or loneliness		Combined effect			**RR=1.51** (95% CI: 1.21–1.88); *k*=7; *N*=n.r.		
Valtorta et al., 2016	Few social network ties, loneliness	Coronary heart disease and stroke	Longitudinal[b]	18+	up to 05.2015	3 to 21 years	16	H
Results:	Few social network ties or loneliness		Coronary heart disease			**RR=1.29** (95% CI: 1.04–1.59); *k*=11; *N*=n.r.		
	Few social network ties		Stroke incidence			**RR=1.32** (95% CI: 1.04–1.68); *k*=9; *N*=n.r.		
Studies on mental health:								
Chang et al., 2017	Living alone, loneliness	Late-life suicidal ideation	Cross-sectional[a,c]	50+	01.2000 - 11.2016	n.r.	7	L
Results:	Living alone		Combined effect			**OR=1.38** (95% CI: 1.19–1.61); *k*=8; *N*=102,401		
	Loneliness		Combined effect			**OR=2.24** (95% CI: 1.73–2.90); *k*=3; *N*=58,482		
Chatterjee et al., 2018	Few social network ties, loneliness	Depression in civilians after 9/11	Longitudinal	43.78 (n.r.)	09.2001 - 07.2016	n.r.	3	L
Results:	Few social network ties or loneliness		Combined effect			**OR=1.68** (99.5% CI:1.13–2.49); k=4; N=27,395		
Chau et al., 2019	Loneliness	Psychosis	Cross-sectional[a,c]	Adults (mainly)	up 10.2018	n.r.	5	M
Results:	Loneliness		Positive symptoms			***r*=.302** (95% CI: .243–.359); *k*=30; *N*=17,832		
			Sub-analysis: clinical populations			***r*=.149** (95% CI: .057–.238); *k*=14; *N*=n.r.		
			Sub-analysis: non-clinical populations			***r*=.389** (95% CI: .232–.526); *k*=5; *N*=n.r.		
			Sub-analysis: mixed populations			***r*=.366** (95% CI: .308–.422); *k*=12; *N*=n.r.		
			Sub-analysis: Paranoia			***r*=.448** (95% CI: .371–.519); *k*=7; *N*= n.r.		
			Sub-analysis: Hallucinations			***r*=.201** (95% CI: .101–.297); *k*=10; *N*= n.r.		
	Loneliness		Negative psychotic symptoms			***r*=.347** (95% CI: .239–.446); *k*=15; *N*=5,567		
			Sub-analysis: clinical populations			***r*=.127** (95% CI: .029–.223); *k*=9; *N*=n.r.		
			Sub-analysis: non-clinical populations			***r*=.479** (95% CI: .351–.589); *k*=4; *N*=n.r.		
			Sub-analysis: mixed populations			***r*=.547** (95% CI: .464–.620); *k*=2; *N*=n.r.		

Choi & Smith, 2013	Few social network ties	Adolescents' smoking behaviors	Cross-sectional	< 19	n.r.	n.a.	3	CL
Results:	Few social network ties		Network position: isolate vs. member			**OR=1.55** (95% CI: 1.32–1.81); *k*=8; *N*=5,067		
			Network position: isolated vs. liaison			**OR=1.49** (95% CI: 1.07–2.07); *k*=8; *N*=5,067		
Erzen & Çikrikci, 2018	Loneliness	Depression	Cross-sectional[a]	Adults	up to 01.2018	n.r.	2	CL
Results:	Loneliness		Combined effect			***r*=.50** (95% CI: .44–.55); *k*=88; *N*=40,068		
			Sub-analysis: clinical populations			***r*=.54** (95% CI: .38–.67); *k*=10; *N*=n.r.		
			Sub-analysis: other populations			***r*=.44** (95% CI: .16–.66); *k*=12; *N*=n.r.		
Evans et al., 2018	Few social network ties	Cognitive functioning	Longitudinal	50+	up to 01.2018	2-24 years	4	M
Results:	Few social network ties		Combined effect			***r*=.054** (95% CI: .043–.065); *k*=51; *N*=102,035		
			Sub-analysis: global measures			***r*=.061** (95% CI: .044–.079); *k*=43; *N*=74,933		
			Sub-analysis: memory			***r*=.050** (95% CI: .028–.072); *k*=13; *N*=35,230		
			Sub-analysis: executive functioning			***r*=.031** (95% CI: .015–.047); *k*=7; *N*=30,528		
Kuiper et al., 2015	Few social network ties, loneliness	Risk of dementia	Longitudinal[b]	60+	up to 07.2012	2 to 15 years	3	M
Results:	Few social network ties		Low social network size			RR=1.17 (95% CI: 0.92–1.48); *k*=5; *N*=7,749		
	Few social network ties		Low level of participation			**RR=1.41** (95% CI: 1.13–1.75); *k*=6; *N*=7,687		
	Few social network ties		Low frequency of contacts			**RR=1.57** (95% CI: 1.32–1.85); *k*=8; *N*=15,762		
	Loneliness		Feeling lonely			**RR=1.58** (95% CI: 1.19–2.09); *k*=3; *N*=3,252		
	Loneliness		Low satisfaction with social network			RR=1.25 (95% CI: 0.96–1.62); *k*=4; *N*=6,207		
Lara et al., 2019	Loneliness	Dementia & mild cognitive impairment	Longitudinal[b]	50+	up to 11.2018	n.r.	6	H
Results:	Loneliness		Combined effect			**RR=1.26** (95% CI: 1.14–1.40); *k*=8; *N*=33,555		
Maes et al., 2019	Loneliness	Social anxiety in children/adolescents	Cross-sectional & longitudinal	15.59 (4.27)	1981 – 06.2016	1.25 to 72 months	4	CL
Results:	Loneliness		Cross-sectional effects			***r*=.46** (95% CI: .43–.48); *k*=98; *N*=41,776		
	Loneliness		Longitudinal/cross-lagged effects			***r*=.12** (95% CI: .04–.21); *k*=10; *N*=3,995		
Mahon et al., 2006	Loneliness	Depression & social anxiety in adolescence	Cross-sectional[a]	Adolescents (11 to 23)	1980 - 2004	n.r.	4	CL

Results:	Loneliness		Depression			***r*=.61** (n.r.); *k*=30; *N*=17,691		
			Sub-analysis: outliers removed			***r*=.55** (n.r.); *k*=18; *N*=6,058		
	Loneliness		Anxiety			***r*=.41** (n.r.); *k*=12; *N*=3,853		
			Sub-analysis: outliers removed			***r*=.35** (n.r.); *k*=10; *N*=2,705		
Michalska da Rocha et al., 2018	Loneliness	Psychosis	Cross-sectional[a,c]	Adults	up to 02.2016	n.r.	4	H
Results:	Loneliness		Combined effect			***r*=.32** (95% CI: 0.20–0.44); *k*=13; *N*=15,647		
Penninkilampi et al., 2018	Living alone, few social network ties, loneliness	Risk of dementia	Longitudinal & case-control	60+	01.2012 – 05.2017	5.9 years	8	L
Results:	Any type of poor social connection		Combined effect			**RR=1.41** (95% CI: 1.21–1.65); *k*=15; *N*=2,330,163		
	Few social network ties		Combined effect			**RR=1.59** (95% CI: 1.31–1.93); *k*=6; *N*=25,373		
	Living alone		Combined effect			**RR=1.41** (95% CI: 1.07–1.84); *k*=4; *N*=5,401		
	Loneliness		Combined effect			RR=1.38 (95% CI: 0.98–1.94); *k*=4; *N*=4,698		
Teo et al., 2013	Living alone	Social anxiety disorder	Cross-sectional[a]	Adults (mainly)	01.1980 - 02.2011	n.r.	4	M
Results:	Living alone		Combined effect			**OR=1.73** (95% CI: 1.34–2.24); *k*=4; *N*=12,831		
			Sub-analysis: large survey studies			**OR=1.70** (95% CI: 1.38–2.10); *k*=3; *N*=12,773		
Xiu-Ying et al., 2012	Living alone	Late life depression	Cross-sectional & longitudinal	55+	1966 - 08.2007	n.r.	3	CL
Results:	Living alone		Cross-sectional effects			**OR=1.44** (95% CI: 1.04–1.99); *k*=16; *N*=34,090		
			Sub-analysis: vs. living with family			**OR=2.59** (95% CI: 1.60–4.20); *k*=5; *N*=12,537		
	Living alone		Longitudinal/cross-lagged effects			RR=1.27 (95% CI: 0.89–1.80); *k*=4; *N*=1,345		
Yuan et al., 2019	Living alone	Post-acute coronary syndrome depression	Longitudinal & case-control	19+	01.1996 - 03.2018	n.r.	4	L
Results:	Living alone		Combined effect			**OR=1.17** (95% CI: 1.12–1.22); *k*=11; *N*=n.r.		

Note: For each result, we specify the type of social connection, the focus of the (sub-)analysis, followed by the reported effect size (in brackets: confidence intervals), as well as included numbers of independent studies and participants. Most meta-analyses included studies both with adjusted and with unadjusted

effect sizes (typically controlling for potential confounders like age, sex, education, socioeconomic status, chronic conditions, depression or anxiety). Unless specified in the table, the authors did not indicate a preference for adjusted or for unadjusted effect sizes. Note that adequate consideration of confounding is also in part reflected in the quality scores. Effect sizes printed in boldface are statistically significant at alpha = 0.05. Abbreviations: n.a.: not applicable; n.r.: not reported; H: High; M: Moderate; L: Low; CL: Critically low.

[a] These studies included different study designs and extracted cross-sectional data or aggregated longitudinal and cross-sectional data.

[b] Effect sizes with adjustment for confounders were preferred in this meta-analysis.

[c] Effect sizes with no or minimal adjustment were preferred in this meta-analysis.

All publications were journal articles in English. Ten meta-analyses reported associations of few social network ties, living alone, and loneliness with physical health outcomes, and 15 with mental health outcomes. Different indicators of social isolation were measured in the included studies. We considered as structural indicators of social isolation *social network ties* defined as an objectively quantifiable variable of one's social contacts irrespective of its perceived quality and *living alone* as an objective characteristic of the living situation. Furthermore, we defined *loneliness* as a quality indictor representing the subjective emotional appraisal of the extent and quality of social relationships.[5] The meta-analyses differed with respect to whether they kept these three measures of social isolation separate of whether they combined them (see Tab. 1).

Figure 1 & Table 1

A total of 276 primary studies were included in the 10 meta-analyses on physical health. The reported results in Table 1 were based on sample sizes ranging from 1,451[17] to 113,374[18] participants, with three meta-analyses not reporting on the sample size. Five meta-analyses were based on longitudinal studies only, one on cross-sectional studies only, and the remaining four on a pooled combination of both cross-sectional and longitudinal studies. Furthermore, social network ties and living alone were examined in 5 meta-analyses on physical health, respectively. Loneliness, on the other hand, was examined in 7 meta-analyses on mental health. Only one of these studies was conducted with children and adolescents.[19] The meta-analyses based on cross-sectional studies revealed a significant association between social isolation and the following health problems: chronic physical complaints in children and adolescents,[19] coronary heart disease and stroke,[20] and frailty in older male (but not female) adults.[18] Additionally, social isolation was associated with malnutrition[21] and

vaccine uptake amongst older adults.[22] One meta-analysis[17] reported mostly non-significant results on a positive association between social isolation and inflammation (acute-phase C-reactive protein and fibrinogen). The meta-analyses conducted with longitudinal studies indicate that social isolation is associated with increased risk of cardiovascular disease,[23] early mortality,[3,24] and hospital readmission in heart failure patients.[25]

The 15 meta-analyses on mental health were based on a total of 416 primary studies. The reported results are based on sample sizes ranging from 1,345[26] to 2,330,163[27] participants, with one meta-analysis failing to report on the sample size. Four of the 15 meta-analyses provided longitudinal data only, one provided cross-sectional data only, and the remaining ten meta-analyses reported on both cross-sectional and longitudinal studies. In addition, social network ties, living alone, and loneliness were examined in 5, 5, and 10 meta-analyses on mental health, respectively. Three meta-analyses focused on studies with children and adolescents.[28-30] The included meta-analyses based on cross-sectional designs reported a significant positive association between social isolation and late-life suicidal ideation,[31] depression in adults,[32] late life depression,[26] psychosis,[28,33,34] smoking behavior in adolescents,[29] depression and social anxiety in childhood and adolescence,[28,30] and social anxiety disorder in adults.[35] The meta-analyses based on longitudinal studies suggest that social isolation is associated with higher risk of depression in adults,[36] post-acute coronary syndrome depression,[37] and dementia and cognitive impairment in later life.[27,38-40] See Table 1 for detailed information.

Study quality

The Intraclass Correlation Coefficient (ICC) of the global quality ratings among the two raters was .83, 95% CI = .62 – .93, indicating good inter-rater reliability. Study

quality was very heterogeneous among meta-analyses both on physical and mental health (see Tab. 1). With respect to the meta-analyses on physical health, the global rating was high in 40%, medium in 10%, low in 40%, critically low in 10% of the meta-analyses. In the 15 meta-analyses on mental health, study quality was rated as high in 13%, medium in 27%, low in 27%, and critically low in 33% of the meta-analyses. Among the AMSTAR-2 criteria, inadequate assessment of risk of bias and/or lack of consideration of risk of bias represented the most frequent critical weaknesses of included meta-analyses.

Discussion

The review clearly demonstrates that social isolation is associated with poorer health. This applies to a range of physical and mental health outcomes and has been found in different populations and contexts. The evidence based on both cross-sectional and longitudinal data is substantial for physical health outcome and even more extensive for mental health outcomes. More specifically, social isolation is linked with chronic physical symptoms, frailty, coronary heart disease, stroke, early mortality, malnutrition, hospital readmission in heart failure patients, and vaccine uptake. With respect to mental health, social isolation is linked with depression in young and adult populations, social anxiety, psychosis, dementia and cognitive impairment in later life, and late-life suicidal ideation.

Strengths and limitations

This is, to our knowledge, the first review to synthesize the existing evidence that has been reported in meta-analyses on the link between social isolation and physical and mental health outcomes. The findings reflect a reasonable number of meta-analyses

which in total included 692 studies. Thus, the overall conclusions of this umbrella review are based on an extensive body of empirical evidence.

However, the review also has several limitations. Firstly, we considered different indicators of social isolation, and our method did not allow us to identify whether one indicator is more relevant than another. Secondly, half of the included meta-analyses for both physical and mental health outcomes had an overall quality rated on AMSTAR-2 as low or critically low, with inadequate consideration of risk of bias being the most frequent critical flaw. Thirdly, the quality of the primary research studies that went into the included meta-analyses also varied and their different methodological shortcomings cannot be adequately considered in this review. Fourthly, the results on the association between living alone and health outcomes need to be interpreted with caution. As reported above, living alone is not necessarily indicative of feeling lonely.[2] Finally, the review included a wide range of health outcomes and did not quantify the strength of the associations for different outcomes.

Implications

The review leaves little doubt that social isolation is linked with poorer physical and mental health. The findings are strengthened by the fact that several meta-analyses were conducted with longitudinal studies. In particular, longitudinal data indicate that social isolation is associated with increased risk of several physical and mental health outcomes, cardiovascular disease, hospital readmission in heart failure patients, early mortality, cognitive impairment, and depression.[3,23-25,27,36-40] However, the findings are all based on observational studies and do not provide evidence on the causal direction of the association. Poor physical and mental health can lead to social isolation, and social isolation can lead to poorer health. For establishing a causal

relationship and examining the strength of the predictive relationship of social isolation and loneliness with health outcomes experimental studies are required, which were not the subject of this review.[4,41] Experimental research with animals, however, suggests that social isolation increases mortality.[42] Furthermore, experimental studies with humans indicate that randomly inducing loneliness or exclusion leads to different health relevant physiological responses than being randomly assigned to a support condition.[42] For most of the considered outcomes in this review, a causal effect of social isolation is plausible and likely to explain at least part of the identified associations. The casual direction is definite in case of the greater risk of isolated people to die early.[3] For an explanation of the damaging effect of social isolation on health outcomes, one may refer to different theoretical models. Theorists from different perspectives have postulated that the impact of social isolation on health is mediated by impairments in social capital,[43] social control,[44] social identification,[45] and social support.[46]

Furthermore, some evidence from randomized controlled trials, however, suggests that expanding the social connections of individuals, e.g., through befriending programs, may indeed improve different health outcomes.[47] Altogether, the literature on interventions to reduce loneliness and social isolation indicates that a policy focus on social connection is a cost-effective strategy for enhancing health at the population level due to the potential pay-offs in health care costs that would otherwise occur. Existing volunteer friendly visiting programs or psychosocial group interventions[48] may need to be redesigned to the point that they can be readily implemented in in accordance with existing rules of physical distancing. Creative programs and interventions to foster social connections, including technology-based social networking programs, are needed.[49] Furthermore, existing policies should

ensure that populations at greater risk, such as the poor and the elderly, receive most support.[1]

All the included studies assessed social isolation as it occurs in a normal societal context. Physical distancing as part of measures to limit the spread of COVID-19 is different from the situations considered in the research synthesized in this review. Firstly, for the vast majority of the population, the required physical distancing leads to a much more pronounced social isolation than what they have experienced before. Secondly, physical distancing is externally imposed and not due to individual life style decisions, lack of material means, poor social skills or other barriers to socialize. And thirdly, physical distancing is requested from people in an overall context of uncertainty that comes with further stressors, health risks, and often a reduced accessibility of health care.

It is important to note that physical distancing is a broad umbrella term that incorporates a wide range of potential measures, with highly divergent implications for social routines. It can include a full lock down and curfew, specific guidelines for meetings and gatherings of people, physical distancing in public, and a recommended or mandatory wearing of face masks. The type, degree, and duration of physical distancing measures have been variable across countries and will affect how isolated different groups in the population become.

One can only speculate as to whether and, if so, to what extent the increased social isolation resulting from physical distancing measures in the current situation will have an even greater impact on health outcomes than has been suggested in this review. Arguably, an even greater impact can be expected for certain risk groups, such as older people who are more threatened by COVID-19 and socially disadvantaged groups (e.g., individuals in need of mental or physical health care or

individuals with low income) who often face even more economic adversity than before the pandemic. Further research is required to identify which populations are at particular risk to suffer health problems as a result of physical distancing and to explore whether the resulting social isolation may – at least to some extent and in some people – be compensated through positive effects of the pandemic, such as strengthened local communities and increased options for online social activities.[47,50]

Conclusions

In governmental decisions about future physical distancing measures, a potential negative impact of the resulting physical isolation on the health of the population needs to be considered. The existing literature suggests that social isolation and loneliness may affect both physical and mental health outcomes and include an excess mortality. However, the potential impact of physical distancing on social isolation and loneliness and ultimately on physical and mental health outcomes need to be thoroughly examined. In addition, the existing knowledge on the association between social connection and physical and mental health should be considered in clinical practice. Finally, more experimental research is needed to increase our understanding of the causal relationship between social connection and physical and psychological well-being.

Figure Captions: Fig.1. Flow diagram of study selection process.

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Authors' Contributions: NM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
NM designed the search strategy with input from AK and TM. NM and AK carried out the literature searches and screening. NM, THH, and TM carried out the data extraction. AK and TM assessed the quality of the included meta-analyses. NM and SP wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

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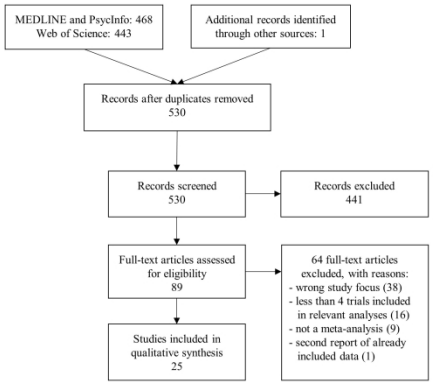

Fig. 1. Flow diagram of study selection process

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A potential impact of physical distancing on physical and mental health. A rapid narrative umbrella review of meta-analyses on the link between social connection and health

Nexhmedin Morina, Ph.D.[1], Ahlke Kip, M.Sc.[1], Thole H. Hoppen, Ph.D.[1], Stefan Priebe, FRCPsych[2], Thomas Meyer, Ph.D.[1]

[1] Institute of Psychology, University of Münster, Münster, Germany

[2] Unit for Social and Community Psychiatry, Queen Mary University of London, London, UK

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* Corresponding Author

Nexhmedin Morina, Ph.D.

Institute of Psychology

University of Münster

Fliednerstr. 21, 48149 Münster, Germany

e-Mail: morina@uni-muenster.de

Abstract

Background: The imperative for physical distancing (mostly referred to as social distancing) during the coronavirus disease 2019 (COVID-19) pandemic may deteriorate physical and mental health. We aimed at summarizing the strength of evidence in the published literature on the association of physical and mental health with social connection via social isolation, living alone, and loneliness.

Methods: We conducted a systematic search in April 2020 to identify meta-analyses using the Medline, PsycINFO, and Web of Science databases. The search strategy included terms of social isolation, loneliness, living alone, and meta-analysis. Eligible meta-analyses needed to report any sort of association between an indicator of social connection and any physical or mental health outcome. The findings were summarized in a narrative synthesis.

Results: Twenty-five meta-analyses met our criteria, of which 10 focused on physical health and 15 on mental health outcomes. The results suggest that lack of social connection is associated with chronic physical symptoms, frailty, coronary heart disease, malnutrition, hospital readmission, reduced vaccine uptake, early mortality, depression, social anxiety, psychosis, cognitive impairment in later life, and suicidal ideation.

Conclusions: The existing evidence clearly indicates that social connection is associated with a range of poor physical and mental health outcomes. A potential negative impact on these outcomes needs to be considered in future decisions on physical distancing measures.

Keywords: Social isolation, living alone, loneliness, physical health, mental health, disease.

Strengths and limitations of this study:

- This rapid umbrella review focuses on a timely and societally relevant issue.
- The systematic literature search was conducted in three major databases from inception up to April 2020 warranting an extensive and up-to-date overview on relevant meta-analyses in the field.
- Quality of included meta-analyses was rated with a standardized measure.
- Different indicators of social connection were included.
- The utilized method did not allow for a quantitative comparison of associations with health outcomes.

Background

The coronavirus 2019 (COVID-19) pandemic poses a global public health threat. In order to slow the spread of the virus by reducing contact rates, governments around the world have taken unprecedented political decisions that have transformed societies. The exact form and extent of these measures have varied, but they always include some type of physical distancing (mostly referred to as social distancing) making it impossible for people to maintain their normal social life.

In many countries, the restrictions have already been in place for several months. Depending on the further course of the pandemic with potential new waves, restrictions might continue for longer periods of time or be re-imposed after periods of loosening or abandoning them. When deciding about imposing, continuing or relaxing measures of physical distancing, governments have to consider and balance different risks. Whilst physical distancing is likely to reduce the risk of spreading the virus, it might generate other risks. These include potential damages to the economy and also possible negative consequences for the health of the population. For a balanced decision on further physical distancing measures, evidence is required on whether the measures are likely to impact on a range of health outcomes.

A recent general population survey revealed that physical distancing can increase the lack of social connection.[1] This may happen when people are prevented from travelling, physical meetings with significant others, and in some cases even from leaving their home other than for essential activities. Social connection has been suggested as an umbrella term representing the extent to which an individual connects to others.[2] Three indicators of social connection are commonly used in research: social isolation, living alone, and loneliness.[3-5] Social isolation is a behavioral measure of a person's social network that can – at least in theory – be objectively

quantified. Living alone describes a basic characteristic of an individual's social situation which can be associated with reduced social relationships, but is not necessarily so.[2] Loneliness, on the other hand, is an individual's subjective assessment of the quality and quantity of their social relationships, reflecting a belief that they have too few or too poor relationships, or both. Accordingly, social isolation and living alone represent structural indicators, whereas loneliness represents a quality measure of social connections.[5,2]

Although these three indicators capture distinct aspects of social connection, they commonly overlap and are associated with each other. Literature suggests that many individuals are socially isolated or lonely or both and that social isolation and loneliness may occur unequally across age groups. For example, Hawkley and colleagues[6] reported that loneliness decreased with age through the early 70s and then increased again. Several studies indicate that at least a fifth of adults report frequent loneliness,[7,8] and that more than 40 percent of adults aged 60 and older report feeling lonely.[9]

The extent to which individuals are socially isolated can have a profound impact on both physical and psychological well-being.[2] Social connection is thought to influence health through behavioral and biological pathways.[10] Several studies demonstrate that social connection is associated with health-relevant behaviors, such as lack of physical activity, poorer sleep, obsessive behavior, as well as neuroendocrine dysregulation,[10] chronic allostatic load,[11] high blood pressure and poor immune functioning.[2,12,13] Furthermore, the magnitude of the effect of social connection on mortality may be equivalent to or exceed the impacts of deleterious behaviors such as excessive drinking or obesity.[4]

Physical distancing may increase lack of social connection and therefore have a negative impact on physical and mental health. For weighing up this potential impact in policy decisions, the existing evidence needs to be considered. Against this background, we conducted a systematic umbrella review to synthesize the evidence on the association between social connection and physical and mental health outcomes. As recommended by the World Health Organization (WHO), we explored relevant meta-analyses by means of a rapid review of evidence.[14]

Methods

To select relevant meta-analyses on the association between social connection and physical or mental health outcomes we conducted a systematic search on 6th April 2020 using the databases Medline, PsycINFO, and Web of Science. We conducted multi-field searches (in titles, abstracts, and key concepts) using the following terms: social isolation, loneliness, living alone, and meta-analy*, which we combined using the Boolean operators “or” plus “and”. The full search string for Medline and PsycINFO was "((TI Loneliness OR AB loneliness OR SU Loneliness) OR (TI social isolation OR AB social isolation OR SU social isolation) OR (TI living alone OR AB living alone OR SU living alone)) AND (TI meta-analy* OR AB meta-analy* OR SU meta-analy*)".

Relevant outcomes included any sort of physical or mental health outcome. We applied no restrictions on age of participants, applied research designs (i.e., cross-sectional, longitudinal), or publication language. Furthermore, we did not apply any limits. We first inspected the title and abstract of all hits and then read full texts of the hits that seemed to meet the aforementioned inclusion criteria. The Preferred

Reporting Items for Systematic Reviews and Meta-analyses reporting standards were followed to document the process of systematic review selection. [15]

Coding of trial characteristics

Systematic reviews with a quantitative synthesis of trial results (meta-analysis) were retained. Two reviewers (NM & THH) coded and extracted from each meta-analysis several objectively verifiable characteristics: Authors and year of publication, inclusion criteria, number of included primary studies, number of participants and their composition by age and health conditions, study design, type of social connection (social isolation/living alone/loneliness) evaluated, clinical outcome, length of follow-up, number of databases searched, and search areas. Furthermore, we extracted the main findings on the association between social isolation/living alone/loneliness and health outcomes (correlation values, odds ratios, or hazard ratios, and the corresponding 95% confidence intervals). With respect to the 95% confidence intervals, both values greater than one (or both values less than one) represent a significant increase (or decrease) as a function of social connection.

Quality Assessment

The quality of included systematic meta-analyses was independently assessed by two reviewers (AK & TM) using A Measurement Tool to Assess Systematic Reviews – 2 (AMSTAR-2).[16] Following the tool's guidelines, the raters assigned one of four global quality ratings (i.e., high, moderate, low, or critically low) after consideration of 16 potential critical and non-critical weaknesses. Items addressing the following criteria were considered as critical: Clear research question including definitions of population, intervention, control group, and outcomes (PICO), adequacy of the literature search, and adequate assessment and/or consideration of risk of bias in the primary studies. Typically, high and moderate ratings reflect the presence of one or

more non-critical weakness, while low and critically low ratings indicate one or more critical weaknesses. Any discrepancies among the independent raters were discussed until consensus was reached.

Results

Selection and characteristics of included studies

Figure 1 displays a PRISMA[15] flow diagram of the publication selection process. After reading 530 abstracts, 89 full text publications were reviewed. The final review resulted in 25 meta-analyses. Relevant characteristics of these meta-analyses are summarized in Table 1.

Table 1: *Overview of the included meta-analyses*

Publication ↳Results:	Social connection	Clinical outcome	Study design	Age: *M* (*SD*), range, or cut-off	Literature search: timespan	Range of follow-up	*N* data-bases searched	Quality score
Studies on physical health:								
Besora-Moreno et al., 2020	Living alone	Malnutrition/ malnutrition risk	Cross-sectional	60+	01.2000 - 12.2018	n.a.	2	L
Results:	Living alone		Combined effect			**OR=1.92** (95% CI: 1.73–2.14); *k*=10; *N*=9,042		
Heidari Gorji et al., 2019	Living alone, social isolation, loneliness	Hospital readmission in heart failure patients	Longitudinal	70.87 (8.62)	up to 11.2018	13 months	6	H
Results:	Any type of poor social connection		Combined effect			**OR=1.55** (95% CI: 1.39–1.73); *k*=13; *N*=6,468		
	Living alone or social isolation		Combined effect			**OR=1.52** (95% CI: 1.24–1.86); *k*=6; *N*=3,812		
	Loneliness		Combined effect			**OR=1.63** (95% CI: 1.31–2.01); *k*=7; *N*=2,656		
Holt-Lunstad et al., 2015	Living alone, social isolation, loneliness	Early mortality	Longitudinal	66.00 (n.r.)	01.1980 - 02.2014	7.1 years	5	L
Results:	Living alone		Unadjusted studies			**OR=1.51** (95% CI: 1.32–1.74); *k*=20; *N*=n.r.		
	Living alone		Studies with multiple covariates			**OR=1.32** (95% CI: 1.14–1.53); *k*=25; *N*=n.r.		
	Social isolation		Unadjusted studies			**OR=1.83** (95% CI: 1.27–2.63); *k*=3; *N*=n.r.		
	Social isolation		Studies with multiple covariates			**OR=1.29** (95% CI: 1.06–1.56); *k*=14; *N*=n.r.		
	Loneliness		Unadjusted studies			**OR=1.49** (95% CI: 1.22–1.84); *k*=8; *N*=n.r.		
	Loneliness		Studies with multiple covariates			**OR=1.26** (95% CI: 1.04–1.53); *k*=13; *N*=n.r.		
Jain et al., 2017	Living alone	Reduced vaccine uptake in older adults	Cross-sectional[a,b]	60+	up to 02.2016	n.r.	2	M
Results:	Living alone		Seasonal influenza vaccine			**OR=1.39** (95% CI: 1.16–1.68); *k*=9; *N*=40,551		
	Living alone		Pneumococcal vaccine			**OR=1.71** (95% CI: 1.20–2.46); *k*=1; *N*=1,702		

Kojima et al., 2020	Living alone	Frailty in older adults	Cross-sectional[b] & longitudinal[b]	60+	2000 - 02.2019	n.r.	1	L
Results:	Living alone		Cross-sectional studies			**OR=1.28** (95% CI: 1.13–1.45); *k*=44; *N*=113,374		
			Sub-analysis: only men			**OR=1.71** (95% CI: 1.49–1.96); *k*=20; *N*=n.r.		
			Sub-analysis: only women			OR=1.00 (95% CI: 0.83–1.20); *k*=22; *N*=n.r.		
			Sub-analysis: >=60, <70 years old			**OR=1.67** (95% CI: 1.51–1.86); *k*=4; *N*=n.r.		
			Sub-analysis: >=80 years old			OR=0.96 (95% CI: 0.69–1.31); *k*=6; *N*=n.r.		
	Living alone		Longitudinal studies			OR=0.88 (95% CI: 0.76–1.03); *k*=6; *N*=38,549		
Maes et al., 2017	Loneliness	Chronic physical conditions in children/adolescents	Cross-sectional[a]	children < 12 and adolescents < 21	1987 – 06.2016	n.r.	4	L
Results:	Loneliness		Combined effect (excl. 3 outliers)			**g=0.17** (95% CI: 0.03–0.30); *k*=40; *N*=3,981		
			Sub-analysis: control group studies			**g=0.13** (95% CI: 0.01–0.26); *k*=23; *N*=2,995		
			Sub-analysis: hearing/visual problems			**g=0.43** (n.r.); *k*=8; *N*=770		
Rico-Uribe et al., 2018	Loneliness	Early mortality	Longitudinal[b]	Mainly 50+	up to 06.2016	n.r.	4	H
Results:	Loneliness		Combined effect			**HR=1.22** (95% CI: 1.10–1.35); *k*=31; *N*=77,220		
			Sub-analysis: only men			**HR=1.44** (95% CI: 1.19-1.76); *k*=7; *N*=5,815		
			Sub-analysis: only women			**HR=1.26** (95% CI: 1.07-1.48); *k*=7; *N*=10,248		
Smith et al, 2020	Social isolation, loneliness	Inflammation markers	Cross-sectional[a]	16+	up to 07.2019	n.r.	5	H
Results:	Social isolation		C-reactive protein: unadjusted studies			***r*=.186** (95% CI: .063–.303); *k*=7; *N*=41,126		
			C-reactive protein: adjusted studies			*r*=.021 (95% CI: .051–.092); *k*=11; *N*=41,911		
			Fibrinogen: unadjusted studies			***r*=.103** (95% CI: .043–.163); *k*=6; *N*=15,421		
			Fibrinogen: adjusted studies			***r*=.039** (95% CI: .011–.067); *k*=6; *N*=22,161		
			Interleukin-6: unadjusted studies			*r*=.267 (95% CI: -.341–.718); *k*=4; *N*=12,291		
			Interleukin-6: adjusted studies			*r*=-.003 (95% CI: -.148–.141); *k*=6; *N*=14,243		
	Loneliness		C-reactive protein: unadjusted studies			*r*=.047 (95% CI: -.003–.098); *k*=8; *N*=17,835		
			C-reactive protein: adjusted studies			*r*=.023 (95% CI: -.018–.065); *k*=6; *N*=19,292		
			Fibrinogen: unadjusted studies			*r*=.006 (95% CI: -.057–.070); *k*=3; *N*=1,806		

			Fibrinogen: adjusted studies			*r*=.037 (95% CI: -.015–.089); *k*=4; *N*=7,672		
			Interleukin-6: unadjusted studies			*r*=.082 (95% CI: -.001–.163); *k*=4; *N*=4,219		
			Interleukin-6: adjusted studies			***r*=.070** (95% CI: .015–.124); *k*=2; *N*=1,451		
Steptoe & Kivimäki, 2013	Social isolation, loneliness	Cardiovascular disease	Longitudinal[b]	n.r.	up to 2011	n.r.	n.r.	CL
Results:	Social isolation or loneliness		Combined effect			**RR=1.51** (95% CI: 1.21–1.88); *k*=7; *N*=n.r.		
Valtorta et al., 2016	Social isolation, loneliness	Coronary heart disease and stroke	Longitudinal[b]	18+	up to 05.2015	3 to 21 years	16	H
Results:	Social isolation or loneliness		Coronary heart disease			**RR=1.29** (95% CI: 1.04–1.59); *k*=11; *N*=n.r.		
	Social isolation		Stroke incidence			**RR=1.32** (95% CI: 1.04–1.68); *k*=9; *N*=n.r.		
Studies on mental health:								
Chang et al., 2017	Living alone, loneliness	Late-life suicidal ideation	Cross-sectional[a,c]	50+	01.2000 - 11.2016	n.r.	7	L
Results:	Living alone		Combined effect			**OR=1.38** (95% CI: 1.19–1.61); *k*=8; *N*=102,401		
	Loneliness		Combined effect			**OR=2.24** (95% CI: 1.73–2.90); *k*=3; *N*=58,482		
Chatterjee et al., 2018	Social isolation, loneliness	Depression in civilians after 9/11	Longitudinal	43.78 (n.r.)	09.2001 - 07.2016	n.r.	3	L
Results:	Social isolation or loneliness		Combined effect			**OR=1.68** (99.5% CI:1.13–2.49); k=4; N=27,395		
Chau et al., 2019	Loneliness	Psychosis	Cross-sectional[a,c]	Adults (mainly)	up 10.2018	n.r.	5	M
Results:	Loneliness		Positive symptoms			***r*=.302** (95% CI: .243–.359); *k*=30; *N*=17,832		
			Sub-analysis: clinical populations			***r*=.149** (95% CI: .057–.238); *k*=14; *N*=n.r.		
			Sub-analysis: non-clinical populations			***r*=.389** (95% CI: .232–.526); *k*=5; *N*=n.r.		
			Sub-analysis: mixed populations			***r*=.366** (95% CI: .308–.422); *k*=12; *N*=n.r.		
			Sub-analysis: Paranoia			***r*=.448** (95% CI: .371–.519); *k*=7; *N*= n.r.		
			Sub-analysis: Hallucinations			***r*=.201** (95% CI: .101–.297); *k*=10; *N*= n.r.		
	Loneliness		Negative psychotic symptoms			***r*=.347** (95% CI: .239–.446); *k*=15; *N*=5,567		
			Sub-analysis: clinical populations			***r*=.127** (95% CI: .029–.223); *k*=9; *N*=n.r.		
			Sub-analysis: non-clinical populations			***r*=.479** (95% CI: .351–.589); *k*=4; *N*=n.r.		
			Sub-analysis: mixed populations			***r*=.547** (95% CI: .464–.620); *k*=2; *N*=n.r.		

Choi & Smith, 2013	Social isolation	Adolescents' smoking behaviors	Cross-sectional	< 19	n.r.	n.a.	3	CL
Results:	Social isolation		Network position: isolate vs. member			**OR=1.55** (95% CI: 1.32–1.81); *k*=8; *N*=5,067		
			Network position: isolated vs. liaison			**OR=1.49** (95% CI: 1.07–2.07); *k*=8; *N*=5,067		
Erzen & Çikrikci, 2018	Loneliness	Depression	Cross-sectional[a]	Adults	up to 01.2018	n.r.	2	CL
Results:	Loneliness		Combined effect			***r*=.50** (95% CI: .44–.55); *k*=88; *N*=40,068		
			Sub-analysis: clinical populations			***r*=.54** (95% CI: .38–.67); *k*=10; *N*=n.r.		
			Sub-analysis: other populations			***r*=.44** (95% CI: .16–.66); *k*=12; *N*=n.r.		
Evans et al., 2018	Social isolation	Cognitive functioning	Longitudinal	50+	up to 01.2018	2-24 years	4	M
Results:	Social isolation		Combined effect			***r*=.054** (95% CI: .043–.065); *k*=51; *N*=102,035		
			Sub-analysis: global measures			***r*=.061** (95% CI: .044–.079); *k*=43; *N*=74,933		
			Sub-analysis: memory			***r*=.050** (95% CI: .028–.072); *k*=13; *N*=35,230		
			Sub-analysis: executive functioning			***r*=.031** (95% CI: .015–.047); *k*=7; *N*=30,528		
Kuiper et al., 2015	Social isolation, loneliness	Risk of dementia	Longitudinal[b]	60+	up to 07.2012	2 to 15 years	3	M
Results:	Social isolation		Low social network size			RR=1.17 (95% CI: 0.92–1.48); *k*=5; *N*=7,749		
	Social isolation		Low level of participation			**RR=1.41** (95% CI: 1.13–1.75); *k*=6; *N*=7,687		
	Social isolation		Low frequency of contacts			**RR=1.57** (95% CI: 1.32–1.85); *k*=8; *N*=15,762		
	Loneliness		Feeling lonely			**RR=1.58** (95% CI: 1.19–2.09); *k*=3; *N*=3,252		
	Loneliness		Low satisfaction with social network			RR=1.25 (95% CI: 0.96–1.62); *k*=4; *N*=6,207		
Lara et al., 2019	Loneliness	Dementia & mild cognitive impairment	Longitudinal[b]	50+	up to 11.2018	n.r.	6	H
Results:	Loneliness		Combined effect			**RR=1.26** (95% CI: 1.14–1.40); *k*=8; *N*=33,555		
Maes et al., 2019	Loneliness	Social anxiety in children/adolescents	Cross-sectional & longitudinal	15.59 (4.27)	1981 – 06.2016	1.25 to 72 months	4	CL
Results:	Loneliness		Cross-sectional effects			***r*=.46** (95% CI: .43–.48); *k*=98; *N*=41,776		
	Loneliness		Longitudinal/cross-lagged effects			***r*=.12** (95% CI: .04–.21); *k*=10; *N*=3,995		
Mahon et al., 2006	Loneliness	Depression & social anxiety in adolescence	Cross-sectional[a]	Adolescents (11 to 23)	1980 - 2004	n.r.	4	CL

Results:	Loneliness		Depression			***r*=.61** (n.r.); *k*=30; *N*=17,691		
			Sub-analysis: outliers removed			***r*=.55** (n.r.); *k*=18; *N*=6,058		
	Loneliness		Anxiety			***r*=.41** (n.r.); *k*=12; *N*=3,853		
			Sub-analysis: outliers removed			***r*=.35** (n.r.); *k*=10; *N*=2,705		
Michalska da Rocha et al., 2018	Loneliness	Psychosis	Cross-sectional[a,c]	Adults	up to 02.2016	n.r.	4	H
Results:	Loneliness		Combined effect			***r*=.32** (95% CI: 0.20–0.44); *k*=13; *N*=15,647		
Penninkilampi et al., 2018	Living alone, social isolation, loneliness	Risk of dementia	Longitudinal & case-control	60+	01.2012 – 05.2017	5.9 years	8	L
Results:	Any type of poor social connection		Combined effect			**RR=1.41** (95% CI: 1.21–1.65); *k*=15; *N*=2,330,163		
	Social isolation		Combined effect			**RR=1.59** (95% CI: 1.31–1.93); *k*=6; *N*=25,373		
	Living alone		Combined effect			**RR=1.41** (95% CI: 1.07–1.84); *k*=4; *N*=5,401		
	Loneliness		Combined effect			RR=1.38 (95% CI: 0.98–1.94); *k*=4; *N*=4,698		
Teo et al., 2013	Living alone	Social anxiety disorder	Cross-sectional[a]	Adults (mainly)	01.1980 - 02.2011	n.r.	4	M
Results:	Living alone		Combined effect			**OR=1.73** (95% CI: 1.34–2.24); *k*=4; *N*=12,831		
			Sub-analysis: large survey studies			**OR=1.70** (95% CI: 1.38–2.10); *k*=3; *N*=12,773		
Xiu-Ying et al., 2012	Living alone	Late life depression	Cross-sectional & longitudinal	55+	1966 - 08.2007	n.r.	3	CL
Results:	Living alone		Cross-sectional effects			**OR=1.44** (95% CI: 1.04–1.99); *k*=16; *N*=34,090		
			Sub-analysis: vs. living with family			**OR=2.59** (95% CI: 1.60–4.20); *k*=5; *N*=12,537		
	Living alone		Longitudinal/cross-lagged effects			RR=1.27 (95% CI: 0.89–1.80); *k*=4; *N*=1,345		
Yuan et al., 2019	Living alone	Post-acute coronary syndrome depression	Longitudinal & case-control	19+	01.1996 - 03.2018	n.r.	4	L
Results:	Living alone		Combined effect			**OR=1.17** (95% CI: 1.12–1.22); *k*=11; *N*=n.r.		

Note: For each result, we specify the type of social connection, the focus of the (sub-)analysis, followed by the reported effect size (in brackets: confidence intervals), as well as included numbers of independent studies and participants. Most meta-analyses included studies both with adjusted and unadjusted effect

sizes (typically controlling for potential confounders like age, sex, education, socioeconomic status, chronic conditions, depression or anxiety). Unless specified in the table, the authors did not indicate a preference for adjusted or for unadjusted effect sizes. Note that adequate consideration of confounding is also in part reflected in the quality scores. Effect sizes printed in boldface are statistically significant at alpha = 0.05. Abbreviations: n.a.: not applicable; n.r.: not reported; H: High; M: Moderate; L: Low; CL: Critically low.

[a] These studies included different study designs and extracted cross-sectional data or aggregated longitudinal and cross-sectional data.

[b] Effect sizes with adjustment for confounders were preferred in this meta-analysis.

[c] Effect sizes with no or minimal adjustment were preferred in this meta-analysis.

All publications were journal articles in English. Ten meta-analyses reported associations of social isolation, living alone, and loneliness with physical health outcomes, and 15 with mental health outcomes. Different indicators of social connection were measured in the included studies. We considered as structural indicators of social connection: *social isolation* defined as an objectively quantifiable variable of one's social network ties irrespective of its perceived quality and *living alone* as an objective characteristic of the living situation. Furthermore, we defined *loneliness* as a quality indictor representing the subjective emotional appraisal of the extent and quality of social relationships.[2] The meta-analyses differed with respect to whether they kept these three measures of social connection separate of whether they combined them (see Tab. 1).

Figure 1 & Table 1

A total of 276 primary studies were included in the 10 meta-analyses on physical health. However, there was some overlap in samples in meta-analyses that examined cardiovascular disease[17,18] and early mortality.[4,19] Steptoe and Kivimäki[17] and Valtorta et al.[18] shared one primary study. In addition, Holt-Lunstad et al.[4] and Rico-Uribe et al.[19] shared 12 primary studies. The reported results in Table 1 were based on sample sizes ranging from 1,451[20] to 113,374[21] participants, with three meta-analyses not reporting on the sample size. Five meta-analyses were based on longitudinal studies only, one on cross-sectional studies only, and the remaining four on a pooled combination of both cross-sectional and longitudinal studies. Furthermore, social isolation and living alone were examined in 5 meta-analyses on physical health, respectively. Loneliness, on the other hand, was examined in 7 meta-analyses on mental health. Only one of these studies was conducted with children and adolescents.[22] The meta-analyses based on cross-sectional studies revealed a

significant association between social connection and the following health problems: chronic physical complaints in children and adolescents,[22] coronary heart disease and stroke,[18] and frailty in older male (but not female) adults.[21] Additionally, social connection was associated with malnutrition[23] and vaccine uptake amongst older adults.[24] One meta-analysis[20] reported mostly non-significant results on a positive association between social connection and inflammation (acute-phase C-reactive protein and fibrinogen). The meta-analyses conducted with longitudinal studies indicate that social connection is associated with increased risk of cardiovascular disease,[17] early mortality,[4,19] and hospital readmission in heart failure patients.[25]

The 15 meta-analyses on mental health were based on a total of 416 primary studies. The reported results are based on sample sizes ranging from 1,345[26] to 2,330,163[27] participants, with one meta-analysis failing to report on the sample size. There was some overlap in samples in the four meta-analyses focusing on cognitive functioning or risk of dementia.[27-30] Kuiper et al.[29] shared two primary studies with Evans et al.[28], four with Lara et al.[30], and three with Penninkilampi et al.[27] Penninkilampi et al.[27] further shared two primary studies Lara et al.[30] Four of the 15 meta-analyses provided longitudinal data only, one provided cross-sectional data only, and the remaining ten meta-analyses reported on both cross-sectional and longitudinal studies. In addition, social isolation, living alone, and loneliness were examined in 5, 5, and 10 meta-analyses on mental health, respectively. Three meta-analyses focused on studies with children and adolescents.[31-33] The included meta-analyses based on cross-sectional designs reported a significant positive association between social connection and late-life suicidal ideation,[34] depression in adults,[35] late life depression,[26] psychosis,[31,36,37] smoking behavior in adolescents,[32] depression and social anxiety in childhood and adolescence,[31,33] and social anxiety disorder in

adults.[38] The meta-analyses based on longitudinal studies suggest that social connection is associated with higher risk of depression in adults,[39] post-acute coronary syndrome depression,[40] and dementia and cognitive impairment in later life.[27,28,30,29] See Table 1 for detailed information.

Study quality

The Intraclass Correlation Coefficient (ICC) of the global quality ratings among the two raters was .83, 95% CI = .62 – .93, indicating good inter-rater reliability. Study quality was very heterogeneous among meta-analyses both on physical and mental health (see Tab. 1). With respect to the meta-analyses on physical health, the global rating was high in 40%, medium in 10%, low in 40%, critically low in 10% of the meta-analyses. In the 15 meta-analyses on mental health, study quality was rated as high in 13%, medium in 27%, low in 27%, and critically low in 33% of the meta-analyses. Among the AMSTAR-2 criteria, inadequate assessment of risk of bias and/or lack of consideration of risk of bias represented the most frequent critical weaknesses of included meta-analyses.

Discussion

The review clearly demonstrates that lack of social connection is associated with poorer health. This applies to a range of physical and mental health outcomes and has been found in different populations and contexts. The evidence based on both cross-sectional and longitudinal data is substantial for physical health outcome and even more extensive for mental health outcomes. More specifically, social connection is linked with chronic physical symptoms, frailty, coronary heart disease, stroke, early mortality, malnutrition, hospital readmission in heart failure patients, and vaccine uptake. With respect to mental health, social connection is linked with depression in

young and adult populations, social anxiety, psychosis, dementia and cognitive impairment in later life, and late-life suicidal ideation.

Strengths and limitations

This is, to our knowledge, the first review to synthesize the existing evidence that has been reported in meta-analyses on the link between social connection and physical and mental health outcomes. The findings reflect a reasonable number of meta-analyses. Thus, the overall conclusions of this umbrella review are based on an extensive body of empirical evidence.

However, the review also has several limitations. Firstly, we considered different indicators of social connection, and our method did not allow us to identify whether one indicator is more relevant than another. Secondly, half of the included meta-analyses for both physical and mental health outcomes had an overall quality rated on AMSTAR-2 as low or critically low, with inadequate consideration of risk of bias being the most frequent critical flaw. Thirdly, the quality of the primary research studies that went into the included meta-analyses also varied and their different methodological shortcomings cannot be adequately considered in this review. Fourthly, the results on the association between living alone and health outcomes need to be interpreted with caution. As reported above, living alone is not necessarily indicative of feeling lonely.[3] Finally, the review included a wide range of health outcomes and did not quantify the strength of the associations for different outcomes.

Implications

The review leaves little doubt that social connection is linked with poorer physical and mental health. The findings are strengthened by the fact that several meta-

analyses were conducted with longitudinal studies. In particular, longitudinal data indicate that social connection is associated with increased risk of several physical and mental health outcomes, cardiovascular disease, hospital readmission in heart failure patients, early mortality, cognitive impairment, and depression.[4,17,19,25,27,39,40,28,30,29] However, the findings are all based on observational studies and do not provide evidence on the causal direction of the association. Poor physical and mental health can lead to lack of social connection, and lack of social connection can lead to poorer health. For establishing a causal relationship and examining the strength of the predictive relationship of social isolation and loneliness with health outcomes experimental studies are required, which were not the subject of this review.[5,41] Experimental research with animals, however, suggests that lack of social connection increases mortality.[42] Furthermore, experimental studies with humans indicate that randomly inducing loneliness or exclusion leads to different health relevant physiological responses than being randomly assigned to a support condition.[42] For most of the considered outcomes in this review, a causal effect of social connection is plausible and likely to explain at least part of the identified associations. The casual direction is definite in case of the greater risk of isolated people to die early.[4] For an explanation of the damaging effect of social connection on health outcomes, one may refer to different theoretical models. Theorists from different perspectives have postulated that the impact of social connection on health is mediated by impairments in social capital,[43] social control,[44] social identification,[45] and social support.[46]

Furthermore, some evidence from randomized controlled trials, however, suggests that expanding the social connections of individuals, e.g., through befriending programs, may indeed improve different health outcomes.[47] Altogether,

the literature on interventions to reduce loneliness and social isolation indicates that a policy focus on social connection is a cost-effective strategy for enhancing health at the population level due to the potential pay-offs in health care costs that would otherwise occur. Existing volunteer friendly visiting programs or psychosocial group interventions[48] may need to be redesigned to the point that they can be readily implemented in in accordance with existing rules of physical distancing. Creative programs and interventions to foster social connections, including technology-based social networking programs, are needed.[49] Furthermore, existing policies should ensure that populations at greater risk, such as the poor, receive most support.[1]

All the included studies assessed social connection as it occurs in a normal societal context. Physical distancing as part of measures to limit the spread of COVID-19 is different from the situations considered in the research synthesized in this review. Firstly, for the vast majority of the population, the required physical distancing leads to a much more pronounced lack of social connection than what they have experienced before. Secondly, physical distancing is externally imposed and not due to individual life style decisions, lack of material means, poor social skills or other barriers to socialize. And thirdly, physical distancing is requested from people in an overall context of uncertainty that comes with further stressors, health risks, and often a reduced accessibility of health care.

It is important to note that physical distancing is a broad umbrella term that incorporates a wide range of potential measures, with highly divergent implications for social routines. It can include a full lock down and curfew, specific guidelines for meetings and gatherings of people, physical distancing in public, and a recommended or mandatory wearing of face masks. The type, degree, and duration of physical

distancing measures have been variable across countries and will affect how isolated different groups in the population become.

One can only speculate as to whether and, if so, to what extent the increased lack of social connections resulting from physical distancing measures in the current situation will have an even greater impact on health outcomes than has been suggested in this review. Arguably, an even greater impact can be expected for certain risk groups, such as socially disadvantaged groups (e.g., individuals in need of mental or physical health care or individuals with low income) who often face even more economic adversity than before the pandemic. Further research is required to identify which populations are at particular risk to suffer health problems as a result of physical distancing and to explore whether the resulting lack of social connections may – at least to some extent and in some people – be compensated through positive effects of the pandemic, such as strengthened local communities and increased options for online social activities.[47,50]

Conclusions

In governmental decisions about future physical distancing measures, a potential negative impact of the resulting physical isolation on the health of the population needs to be considered. The existing literature suggests that social isolation and loneliness may affect both physical and mental health outcomes and include an excess mortality. However, the potential impact of physical distancing on social isolation and loneliness and ultimately on physical and mental health outcomes need to be thoroughly examined. In addition, the existing knowledge on the association between social connection and physical and mental health should be considered in clinical practice. Finally, more experimental research is needed to increase our understanding

of the causal relationship between social connection and physical and psychological well-being.

Figure Captions: Fig.1. Flow diagram of study selection process.

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NM designed the search strategy with input from AK and TM. NM and AK carried out the literature searches and screening. NM, THH, and TM carried out the data extraction. AK and TM assessed the quality of the included meta-analyses. NM and SP wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

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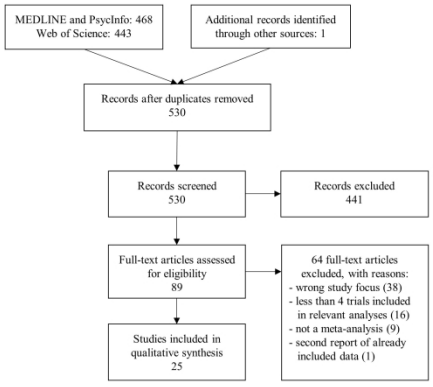

Fig. 1. Flow diagram of study selection process

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MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate		

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results		
Assessment of heterogeneity		
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
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Justification for exclusion (eg, exclusion of non–English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
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