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Abstract

Objective
Continuity of care is a longstanding feature of health care, especially general practice. It is associated with increased patient satisfaction, increased take-up of health promotion, greater adherence to medical advice and decreased use of hospital services. This review aims to examine whether there is a relationship between the receipt of continuity of doctor care and mortality.

Design
Systematic review without meta-analysis.

Data sources
Medline, Embase and the Web of Science, from 1996 to August 2016

Eligibility criteria for selecting studies
Peer-reviewed primary research articles, published in English which reported measured continuity of care received by patients from any kind of doctor, in any setting, in any country, related to measured mortality of those patients.

Results

Of the 682 articles identified in searches, 19 fulfilled the eligibility criteria. The studies were all cohort or cross-sectional and most adjusted for multiple potential confounding factors. These studies came from nine countries with very different cultures and health systems. We found such heterogeneity of continuity and mortality measurement methods and time frames that it was not possible to combine the results of studies. However, 15 (78.9%) high quality studies reported statistically significant reductions in mortality, 13 (68.4%) all-cause mortality, with an increased level of receipt of continuity of care, three showed no association and one demonstrated mixed results. These significant protective effects occurred with both specialist and generalist doctors.

Conclusions

This first systematic review reveals that increased continuity of care by doctors is associated with lower mortality rates. Although all evidence is observational, patients across cultural boundaries appear to benefit from continuity of care with both generalist and specialist doctors. Many of these articles called for continuity to be given a higher priority in healthcare planning. Despite substantial, successive, technical advances in medicine, interpersonal factors remain important.

Systematic review registration

PROSPERO 2016:CRD42016042091

Strengths and limitations of this study

- The first systematic review of continuity of care and mortality
- We included studies working with patients with all conditions, of all ages and of all stages of conditions.
- We included articles investigating continuity with all kinds of doctor in any health system.
- We included articles using any clearly defined measure of continuity of care.
- A meta-analysis was not possible due to heterogeneity of continuity and mortality measures.

Introduction

Medical science has advanced rapidly since the early nineteenth century. Major advances from the germ theory to the sequencing of the human genome have together generated much deeper understanding of the pathophysiology of disease with improved prevention and treatment. However, all these advances are mostly related to physical factors. Research on human aspects of medical care has lagged.

One example of this is continuity of care. The definition of continuity of care used in this study is repeated contact between an individual patient and a doctor. Such repeated contact gives patients and doctors the opportunity for improved understanding of each other's views and priorities.

Much is known about how continuity of care in general practice fosters patient satisfaction,[1] improves health promotion,[2] increases adherence to medication,[3] reduces hospital use,[4]

and ameliorates socio-economic disadvantage.[5] But important as these are, death is clearly the most important and serious of all outcomes.

Since 2010, individual studies have emerged investigating whether continuity of care is associated with reduced mortality.[6-25] These reports represent a new development, underlining the interpersonal component of medical care.

Research question

Are higher levels of continuity of doctor care, in any setting, with any patient group, associated with changed mortality?

Methods

Protocol and registration

The protocol for this systematic review was registered on PROSPERO: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042091

Search strategy and selection criteria

For inclusion in this systematic review (without meta-analysis), articles must have been published in the peer-reviewed literature, in the last 20 years, in English. We searched the databases of *Medline*, *Embase* and the *Web of Science* from 1996 to August 2016 by searching for 'continuity' OR 'continuity of care' together with terms for a medical doctor/physician and terms indicating death or mortality in the title or abstract (see supplemental information- example search strategy). In addition, references of articles selected were hand-searched for additional relevant citations.

Experimental and observational study designs were considered including controlled trials, cohort studies (prospective and retrospective) and case-control studies. Systematic reviews and meta-analyses were excluded. Study participants could include any patient group, including entire populations or groups of patients with a specific disease or other feature.

Articles must have compared measured degrees of continuity of care with doctors (of any kind) to mortality rates. Any valid measure of continuity was considered, including continuity being lost or absent and articles where the continuity measure was a single appointment or visit by a GP/family physician during a hospital stay. Articles about organisational continuity and general staffing numbers were excluded.

As an outcome measure, any measure of mortality was accepted, i.e. all-cause, date/age-limited or cause-specific. When complications or hospital admissions were combined with death rates, we sought a separate measure of mortality alone. If this was not available, studies were excluded.

Two pairs of reviewers checked the search results and decided independently whether papers met the eligibility criteria. Initially, the title and abstract of each citation was screened. The full texts of selected articles were then examined. Disagreements were resolved by discussion and PHE independently had the deciding vote.

Data items

The variables and outcomes extracted included basic information: authors, date and country. We also extracted study design, study population (any particular condition, setting, age group, any other inclusion or exclusion criteria and selection method), numbers of patients, measure of continuity, length of continuity measurement and doctor type (generalist doctor including GP, family physician and primary care physician or specialist). We extracted the period of time for the mortality measurement, and any overlap with or interval between mortality and continuity measurement periods. We also extracted whether mortality was all-cause or a disease-specific cause or limited to a particular group, how mortality was assessed and confounding factors tested or accounted for. We also extracted an estimation of any association found, with risk or odds ratios where possible and whether higher continuity was linked to an increased or decreased mortality risk. Data were extracted independently by two reviewers (of DJPG, EW, AT and KSL), using the data extraction table designed for this review. Disagreements were resolved as above.

Risk of bias

The quality and risk of bias was assessed independently for individual studies by two reviewers using the Newcastle-Ottawa Scale[26] We also assessed relevant areas of bias in terms of the timing of continuity and mortality measurement and confounding factors considered. For continuity of care and mortality there is a particular potential for bias in that the worsening of health status before death may cause either decreased or increased continuity of care[27] so we noted whether this had been considered and adjusted for in study design. In terms of bias across studies, we considered publication bias and reporting bias in terms of whether mortality was the primary outcome.

Data analysis

Studies were analysed for a relationship between continuity of care and mortality rates and whether this relationship was an inverse one (i.e. greater continuity of care led to lower mortality rates) or not. For each study we sought a risk metric (i.e. relative risk, hazard or odds ratio) from an adjusted model of data analysis in order to minimise the risk of selection bias and confounding. Where these statistical metrics were not reported we provided any other available comparison measure.

Results

Study selection

After removal of duplicate results, 682 peer-reviewed publications were identified. No previous systematic reviews or trials on this subject were found. Of the 682 papers identified, 36 papers were selected for full text review (Figure 1). Articles were then excluded if continuity was not clearly measured or was the dependent variable[28-33], if the continuity of care measure was not clearly with a doctor or doctors only[6,34-40] and if mortality was not analysed or not analysed separately at any point[41-43] (for example if it was expressed only as a composite outcome with hospitalization). This left 19 studies for inclusion.

Study Characteristics

As shown in Table 1, the majority of included reports (13, 68.4%) were of retrospective cohort studies, often using insurance data. There were three prospective cohort, and three cross-sectional studies. No randomised controlled trials were found. A number of the cohort studies included large numbers of patients (median 13,400). All of the reports were published since 2010 including four in 2016. The studies were carried out in nine different countries; the majority were from North America (five-Canada, four-USA). Seven were from Europe (three-England, two- France and one each- Croatia and the Netherlands). There was one each from Israel, South Korea and Taiwan.

Nine (47.6%) of the studies investigated continuity with a GP/family physician/primary care physician, two were with specialists only[9,12] and eight included continuity with doctors of any kind. Six studies (31.6%) selected patients during or following an index hospitalization.[9,10,19,21-23] Four studies studied patients with diabetes[16,17,24,25] and three studies included older patients.[8,18,25]

The continuity measures used are reported in Table 1. The most common measure used was the UPC (Usual Provider of Care) index which was used in nine studies (47.6%).[8,9,14,17,19,21,23-25] Five studies used more than one measure, some only for sensitivity analysis.[8,14,19-21] One study[8] was designed to compare the association of different continuity measures with outcomes, including mortality. One article[10] used the occurrence of a supportive visit by a family physician to a patient in hospital and another[11] simply took loss of contact as meaning loss of continuity. Three studies[7,13,15] used the results of a question or questions from the annual UK national General Practice Patient Survey (GPPS).

The length of time over which continuity was measured (when not a survey response or hospital visit indicating a relationship) varied greatly between studies, from a single weekend in hospital[9] up to 17 years[18]. The median length of continuity measurement was 2 years (IQR 2.5).

Most studies (17, 89.5%) reported all-cause mortality. One study [7] investigated premature mortality; under the age of 75. Another[13] used premature coronary heart disease mortality as the primary outcome. The length of time for recording deaths also showed a large variation between studies, from 30 days to up to 21 years. The median follow up time was 3 years (IQR 4.25).

Most of the studies investigated a large number of potential confounding factors (Table 1). All studies working at the level of individual patients included some measure of health status including LACE index, co-morbidities, previous healthcare usage and other measures. Most studies looked at age and sex and 13 (68.4%) used a measure of deprivation, social status or income.

Table 1. Studies investigating the link between continuity and mortality that meet the inclusion criteria, ordered by study design.

First author and year of publication	Country of origin	Patients	number of patients if applicable	Continuity measure	Continuity with	length of time continuity measured	Confounding factors checked and/or adjusted for	Mortality measure	Quality score	Mortality primary outcome ?	length of time mortality counted
Cerovečki 2013[11]	Croatia	With opioid dependence, treated with methadone in family medicine setting	287	7	Family physician	12 yrs	A,B,M,O,S	All cause	8.5	Yes	12 yrs
Spatz 2014[22]	USA	18 yrs+, hospitalized with acute myocardial infarction	2,454	8	Doctor	N/A	A,B,C,D,E,F,G,I,J,M,O,T	All cause	9	Yes	12 months
van Walraven 2010[23]	Canada	18 yrs+, discharged into community from medical or surgical services of 11 Ontario hospitals	3876	1	Physician who saw patient before, during and/or after hospital stay	6 months	A,B,H,L,N,O	All cause	9	Yes	6 months
Bentler 2014[8]	USA	65 yrs+ Community residing Medicare beneficiaries who completed NHHSUQ survey, not in managed care, not in MMC plan.	1219	1, 2, 3, 5, 8	Physician	1-2yrs	A,B,C,D,E,F,G,H,I,K,M,N,O	All cause time to death	9	Yes	up to 5 yrs
Blecker 2014[9]	USA	18 yrs+, hospitalised at least 2 days including at least one at weekend	3391	1	Discharge physician	2 days	A,B,C,K,N,O,T	In hospital	8	No	Length of hospital stay
Brener 2016[10]	Canada	18 yrs+, discharged from hospital into community, family physician has history of hospital visits.	164059	9	Family physician	N/A	A,B,D,L,O,Q	All cause	9	Yes	90 day Post discharge
Hoertel 2014[12]	France	in CNAMTS insurance fund, saw a psychiatrist regularly	14515	2	Psychiatrist	3.5 yrs	A,B,D,K,N,O	All cause	8.5	Yes	3 yrs
Leleu 2013[14]	France	NHI reimbursement patients, >2 visits in 6 months	325742	1, 2	Primary care physician/GP	3 yrs	A,B,D,K	All cause	9	Yes	3 yrs
Liao 2015[16]	Taiwan	31-99 yrs, with type 2 diabetes	89428	6	Any physician	1 yr	A,B,H,K,N,O,P,U	All cause	8.5	No	4-9 yrs
Lustman 2015[17]	Israel	40-75 yrs, with type 2 diabetes, remained in area, saw primary care provider >3x	23679	1	Primary care physician/GP	2 yrs	A,D,H,K,M,N,O	All cause, diabetes related causes	8.5	Yes	2 yrs
Maarsingh 2016[18]	The Netherlands	55–85 yrs, data available.	1712	3	GP	17 yrs	A,B,D,E,F,G,K,M,Q,O	All cause	9	Yes	21 yrs
McAlister 2013[19]	Canada	20 yrs+ DC from hospital with 1st time heart failure	16,855	0, 1	Physician who saw patient x2 in yr before or 1x during admission	N/A	D,K,O,P,Q,R	All cause	9	Composite	3m/6m
Shin 2014[20]	South Korea	20 yrs+, in Korean National Health Insurance, new diagnosis of hypertension, diabetes, hypercholesterolemia or their complications.	47433	2, 4, 5	Physician	2 yrs	A,B,D,F,K,N,Q,U	All cause	9	Yes	up to 5 yrs

Sidhu 2014[21]	Canada	"Adults" treated and released from 93 Emergency departments with first time diagnosis of Heart Failure	12,285	0, 1	Physician who saw patient x2 in year before or 1x during admission	30 days	A,B,G,K,O,P, Q,N	All cause	8.5	Composite	12months but only give separate data for deaths for 30 days
Weir 2016[24]	USA	20 yrs+, with incident diabetes and at least 2 years insurance.	285231	1	physician who saw patient the most	2 yrs	A,B,D,G,H,K, O	All cause	8.5	Composite	1 yr
Worrall 2011[25]	Canada	65 yrs+, with diabetes, 2+ fee-for-service family physician visits.	305	1	Family physician	3 yrs	A,B,N	All cause	7	Yes	3 yrs
Baker 2016[7]	England	Registered with 7858 general practices, with complete data, in England	N/A	8	GP	N/A	C,D,F,G,J,P	premature- ratio observed to expected, age < 75	8	Yes	N/A
Honeyford 2013[13]	England	Registered with 229 general practices in the east Midlands between April 2006 and March 2009	just under 1.7 million	8	GP	N/A	A,B,C,D,F,G,P ,U	CHD under 75 and all age	8	Yes	3 yrs
Levene 2012[15]	England	18 yrs+, registered with GP for at least 6/12 months of the year	51.8 million	8	GP	N/A	A,B,C,D,F,O,P	All cause, COPD, all cancer, CHD	9	Yes	2 yrs

F	Smoking	
1	G	Chronic conditions
2	H	Prior hospitalisation
3	I	Insurance
4	J	Acute conditions
5	K	Co-morbidity (including Charlston index)
6	L	LACE index (risk of 30 day re-admission or death after hospital discharge)
7	M	Marital/ relationship status
8	N	Number of healthcare visits/service intensity
9	O	Other healthcare history
0	P	Practice characteristics
Q	Location	
A	R	Length of hospital stay
B	S	Treatment plan
C	T	Timing of admission
D	U	Other
E		

Results of individual studies

Of the 19 studies, 15 (78.9%) showed that greater of continuity of care was significantly associated with lower mortality. Of these, 13 (68.4% of the 19) were with lower all-cause mortality (Table 2). Two studies found no association of greater continuity of care with subsequent mortality during[9] or following[23] a hospital stay. One study found that continuity was not significantly associated with mortality except in GP practices in the least deprived areas.[7] One study[8] investigated a range of continuity measures. They found that all insurance claims-based measures showed that higher levels of continuity were associated with higher mortality rates but greater continuity as reported by patients was associated with reduced mortality. This is the only study showing any association of increased continuity with increased mortality.

Due to the heterogeneity of study continuity and mortality measurements, it was not possible to combine them to produce an estimate of effect size however Table 2 shows the risk, odds or hazard ratios from individual studies where available.

Table 2. Outcome measures of studies investigating the association of continuity of care with mortality

First author and year of publication	Ratio (if available)	Other result	95% CI	for measure	Continuity associated with mortality?	Results summary
Cerovečki 2013[11]	12.6*		3.001-53.253	OR, loss of COC	Yes	Loss of continuity of care one predictor of fatal outcome.
Spatz 2014[22]	1.92*		1.19-3.12	AHR, No usual source of care vs strong usual source of care (USOC) relationship	Yes	In multivariable analysis, having no USOC associated with higher 12-month mortality
van Walraven 2010[23]	1.03		0.95-1.12	AHR, increase of 0.1 in continuity score, preadmission physician	No	No significant association found for death risk with continuity with any doctor type studied
	0.87		0.74-1.02	AHR, increase of 0.1 in continuity score, hospital physician		
	0.97		0.89-1.06	AHR, increase of 0.1 in continuity score, post-discharge physician		
Bentler 2014[8]	2.25†		1.33-3.81	AHR above vs below mean patient-reported care site continuity	Yes	Patient-reported duration continuity had significant, protective association with time to death. Seven claims-based continuity of care indicators and one patient-reported measure (Site continuity) showed higher continuity associated with increased death hazard
	0.54*		0.37-0.8	AHR, highest v lowest tertile patient-reported duration continuity		
	2.3†		1.56-3.38	AHR,highest v lowest tertile, UPC		
	1.8†		1.12-2.88	AHR,highest v lowest tertile, Inverse number of providers		
	1.69†		1.13-2.52	AHR,highest v lowest tertile, MMCI		
	1.7†		1.12-2.59	AHR,highest v lowest tertile, Ejlertsson's index K		
	2.33†		1.56-3.49	AHR,highest v lowest tertile, Bice Boxerman CoC		
	1.98†		1.23-3.21	AHR,highest v lowest tertile, MCI		
	2.35†		1.59-3.49	AHR,highest v lowest tertile,sequential continuity		
Blecker 2014[9]	0.72		0.29-1.8	AOR, UPC 1 (complete continuity) vs 0, no continuity	No	Increased weekend UPC was significantly associated with decreased mortality in unadjusted analysis. No association after multivariate adjustment.
Brener 2016[10]	0.87*		0.82-0.93	AOR, visited vs not, 90 day post discharge	Yes	In unadjusted model, visited patients more likely to die at 90 days. In unadjusted model, visited patients less likely to die at 90 days
	0.88*		0.81-0.86	AOR, visited vs not, 30 day post discharge		
Hoertel 2014[12]	0.83*		0.83-0.83	AHR, 0.1% increase in COC index	Yes	0.1 increase in COC index associated with decreased likelihood of death.
	0.53*		0.52-0.54	AHR, perfect continuity vs imperfect continuity		
Leleu 2013[14]	0.96*		0.95-0.96	HR, 0.1 increase in COC	Yes	Increase in the COC index associated with decrease in death risk
Liao 2015[16]	*	Significant trend observed (P<0.001, test for monotonic trend)		decreasing consistency in medical care seeking behaviour with decreasing adjusted survival	Yes	A significant monotonic trend was observed between decreasing consistency in medical care–seeking behaviour (from high consistency to low consistency) and decreasing multivariate-adjusted survival
Lustman	0.59*		0.5-0.7	OR, high vs low UPC, measured at same time	Yes	Patients with a high UPC had lower risk of mortality. Not

2015[17]	0.7*		0.56-0.88	OR, high vs low UPC, measured in successive years		affected on adjusting for background characteristics.
Maarsingh 2016[18]	1.2*		1.01-1.42	HR, lowest vs highest COC	Yes	In final model, participants in lowest COC category showed greater mortality than those in maximum.
McAlister 2013[19]	0.86			HR, familiar vs unfamiliar (our calculation, CI not available)	Yes	After 6 months death HR for familiar Dr 0.66 (95%CI 0.61-0.71) and 0.77 (0.68-0.88) with unfamiliar vs no follow up. At 3 months 1.6% of those who had a visit with a familiar Dr died, 3.3% who only saw an unfamiliar Dr, P<0.001
Shin 2014[20]	1.13*		1.05-1.21	AHR, below vs above median most frequent provider	Yes	Above median continuity associated with lower all-cause mortality using 3 different measures
	1.13*		1.05-1.21	AHR, below v above median MMCI		
	1.12*		1.04-1.21	AHR, below v above median COC		
Sidhu 2014[21]	*	1.9% vs 1.4%		% mortality- follow up by unfamiliar or familiar physician	Yes	More died with follow up with unfamiliar physician compared with those with at least one visit with familiar physician.
Weir 2016[24]	0.75*		0.61-0.94	AOR, high v low UPC	Yes	High UPC associated with decreased mortality
Worral 2011[25]	*	9.0% vs 18.1% (P=0.025, χ^2)		% mortality-high vs low continuity group.	Yes	Proportion of people dying significantly lower in high-continuity group
Baker 2016[7]		21 deaths	−16 to 63	Potential reduction in premature deaths in England in 1 year if there is a change of 1 percentile of patients expressing trust in their doctor	No	Continuity not associated with mortality (except in less deprived practices in a separate subgroup analysis).
		-49 deaths	−250 to 156	Potential reduction in premature deaths in England in 1 year if there is a change of 1 percentile of patients able to get an appointment in advance		
Honeyford 2013[13]	0.994*		0.989-1	IRR,1% change in survey response	Yes	An increase in % of patients recalling being able to see their preferred GP was associated with decreased mortality
Levene 2012[15]	0.999		0.997-1.01	IRR, All-cause mortality	Depends on mortality measure	No significant association with all-cause mortality. An increase in the % of patients recalling being better able to see their preferred doctor was associated with decreases in COPD mortality and in all cancer mortality.
	0.997*		0.995-0.999	IRR, All cancer mortality		
	0.999		0.995-1.07	IRR, Coronary Heart Disease mortality		
	1.0002		0.99-1.01	IRR, Stroke mortality		
	0.993*		0.98-0.998	IRR, COPD mortality		

Key
* Significant result showing higher levels of continuity associated with lower mortality
† Significant result showing higher levels of continuity associated with higher mortality

Abbreviations
HR- Hazard ratio
OR- odds ratio
AHR- adjusted hazard ratio
AOR- adjusted odds ratio
IRR- incident rate ratio
UPC- usual provider of care index
COC- continuity of care index

Risk of bias within studies

Using the Newcastle-Ottowa scale,[26] all 19 studies were rated as high quality, with nearly half (9 studies, 47.6%) gaining maximum scores from both reviewers independently (Table 1, Supplemental Table). No study was scored less than 7 out of 9 by any reviewer. As all these studies were cohort or cross-sectional studies, they tested for associations only. However, most involved statistical analyses for a wide range of potential confounding factors (Table 1 and above).

The specific bias of reverse causality between the healthcare-related events that might occur before death was discussed in 12 (63.2%) of the studies. Three cohort studies did not discuss reverse causality.[11,18,25] However, all but one[25] of the studies included a measure of health/disease status as a potential confounding factor and some included several detailed measures of these in their models.

Four of the studies had a design which meant there was no overlap between the time for continuity measurement and the period during which deaths were counted.[8,16,20,24] Six studies have complete[11,14,17,21,23,25] and four partial overlap of these periods.[9,12,18,19] four studies included additional analyses which either eliminated the overlap[17] or introduced a lag time[12,14,20] between continuity and mortality measurement periods. In each of these additional analyses, continuity was still found to be significantly associated with mortality. One long term study[18] calculated survival from the date of the last continuity measurement and stratified by the length of time in the study. Five studies[12,14,19,20,21] used their continuity score as a time dependant variable in the model.

Risk of bias across studies

There is a risk of publication bias. It may be that reports showing no effect are less likely to be published. However, two showed no association. In two, mortality was not the primary outcome and in six, it was part of a composite outcome. For 12 studies, mortality was not the only outcome. In seven studies the association of two or more factors, including continuity, with outcomes was tested. Continuity and mortality as exposure and outcome respectively, are reported in a range of studies, including where testing this association was not the primary aim.

Discussion

Principal Findings

In a substantial majority of studies (15, 78.9%) meeting the selection criteria, higher levels of continuity of care with doctors were associated with lower mortality rates. Two others, finding no significant association, had very short timescales for measurement of continuity, to the extent that the strength of any patient-doctor relationship was potentially questionable. The other study showing no significant association with all-cause mortality was cross-sectional and the measurement methods relate to questions on a national survey about seeing a particular GP, again not necessarily indicative of a strong patient-doctor relationship.

One study[8] found that for claims-based measures of continuity, increased mortality was associated with higher levels of continuity of care. However in the same study, higher levels of patient-reported continuity were associated with lower mortality rates. This emphasises the interpersonal relationship between patient and doctor as claims based measures only give numbers of contacts and do not directly measure the quality of the relationship.

The effect sizes are generally small (Table 2) but these are in the same range as some treatment effects compared to placebo, as very large, repeatable effects on mortality are rare.[44] In addition, for some studies included in this review, effect sizes are calculated using very small increments in the continuity measure.

Strengths and weaknesses of the evidence

All the studies found investigating the association of continuity of care with mortality were observational in nature, although the majority are high quality cohort studies including three prospective cohort studies. The issue of reverse causality applies to all the evidence presented here. This could bias an association between continuity of care and mortality in either direction. As patient health worsens when approaching death, continuity of care may deteriorate for many reasons e.g. patients moving areas to accommodate increased health needs, the need to see more specialists, or a loss of ability to obtain and attend appointments. Alternatively, deterioration of health could lead to a concerned doctor ensuring that the patient receives more continuity of care. For the cross-sectional studies there is also potential for confounding due to practice-level factors.

There have been randomised controlled trials into continuity of care but none on existing relationships or lasting longer than a year.[45-47] RCTs are desirable but with pre-existing long-term human relationships, like marriage and parent-child relationships, prospective randomisation is never possible. Some doctor-patient relationships last for decades and become highly personal and are therefore RCTs are unethical or impractical. Observational studies which control rigorously for confounding factors are the best evidence available.

Of the 13 cohort studies finding an association of higher continuity with lower mortality, most studies attempt to at least partially account or control for reverse causality in their study design or analysis. Most controlled for differences in health status and risk

factors.[10,11,12,14,17,18,19,22,24] Some ran analyses measuring continuity and mortality in separate years,[8,12,14,16,20,17,22,24] or with a lag.[12,14,20] This method, particularly the lag between measurements, should help to prevent bias caused by rapid worsening prior to death. However, three smaller cohort studies showing this association[11,18,25] did not discuss this kind of reverse causality although one[18] nevertheless made several adjustments for health status and calculated survival from the date of the last continuity measurement. Measuring continuity and mortality over separate time periods is also one way of eliminating the potential bias caused by those who survived longer having more time to accrue continuity. Another way of reducing this is to model continuity as a time-dependant variable which was the case in five studies.[12,14,19,20,21]

There is a risk of publication bias as we included only published studies. However, three of the published studies included in this review show no significant association. In addition, mortality as an outcome is of such clear importance that it is often reported even when not the only or primary outcome so reporting bias is possibly also less likely.

All studies included were rated as high quality, using the Newcastle-Ottawa scale.
Several of the articles reported on studies using very large cohorts. The studies came from a number of different countries with different healthcare systems and cultures. Continuity of care in the studies included that received from specialist as well as generalist doctors, showing that the effect is not limited to one branch of medicine or health system.

As continuity research is an emerging field, no consensus on the best way to measure it has been reached. The measure used most was the UPC index which does not take into account the total number, frequency or sequence of visits and is therefore a proxy measure for the patient-doctor relationship.[8]

Doctors have been studied as a discrete category in numerous studies and data systems usually allow them to be separately studied. The group studied included family doctors/GPs, physicians and psychiatrists so was already heterogeneous so expanding this to other professional groups would have complicated interpretation. As doctors are the most highly-trained health professionals with the most influence over decisions, it is reasonable to assume that if interpersonal contact affects mortality, it is most likely to occur with doctors. Therefore we eliminated articles, some with significant reductions in mortality, that measured continuity in relation to mixed profession teams or to other health professionals.[6,35-37,39] This is the first systematic review investigating whether continuity of doctor care is associated with reduced mortality. We expect this to encourage studies with different selection criteria; for example for continuity with other healthcare professionals.

Possible mechanisms and implications

This review, finding that increased receipt of continuity of care is associated with reduced mortality in the majority of studies comes after it has been shown that continuity of care is associated with increased patient satisfaction,[1] increased take-up of health promotion[2] and reduction in use of hospitals.[3] It therefore fits well with such earlier work. It is only recently that large databases have become available and long-term cohort studies have reported to enable effective investigation into links between continuity and mortality.

These known associations suggest possible mechanisms in that greater uptake of evidence-based preventative medicine such as immunisations as well as better concordance with treatments are likely to reduce mortality. In addition to this possible effect, a doctor who repeatedly sees a patient gathers more information and understanding, which Hjortdahl (1992)[48] described as "accumulated knowledge", than a doctor for whom the patient is a stranger. In most cases, better decisions are made when there is more information available. Continuity of care is associated with patients perceiving that the doctor has become more responsive.[49] Patients then disclose more and medical management is more likely to be tailored to the needs of the patient as a person (patient-centred care). The increased patient satisfaction may also be associated with an "optimism" boost to health.[50] The cumulative impact of these multiple gains may then be reflected in reduced mortality. Historically continuity of care has been considered a feature of the practice of medical generalists and featured in the job descriptions of the general practitioner.[51,52] Recent studies included in this review found that continuity is associated with reduced mortality with both specialist physicians[16,20] and psychiatrists[12] too.

Although this evidence is observational, with fifteen of the nineteen studies showing significant reductions in mortality with continuity of care, the clear preponderance of evidence is in favour of the association. Three studies show no significant association and one[8] had mixed results but no study exclusively showed an association of higher continuity of care with higher mortality rates. Although there are difficulties in carrying out controlled trials on this subject, a few, with interventions to increase continuity of care, have been successful[45,46] and this could be attempted more widely. The presence of this association in nine countries, across three continents, and in very different populations and health care systems implies a basic human effect. The policy implication as many studies noted is prioritising continuity of care.

For 200 years, medical advances have been mainly technical and impersonal, which has reduced attention to the human side of medicine. This systematic review reveals that despite numerous technical advances, continuity of care is an important feature of medical practice, and potentially a matter of life and death.

Contributors

DJPG conceived the idea for the systematic review. KS-L wrote the protocol with input from other authors and submitted it to PROSPERO. AT, EW and KS-L carried out database searches. DJPG, KS-L, AT and EW carried out article selection, data extraction and assessing article quality. PHE had the deciding vote in article selection, data extraction and assessing article quality. KS-L carried out data analysis. PHE, DJPG and KS-L interpreted the data. All authors wrote and edited the manuscript. All authors approved the manuscript for publication.

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Transparency statement

PHE is guarantor of the paper and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Figure legend:

Figure 1. Study selection flow diagram.

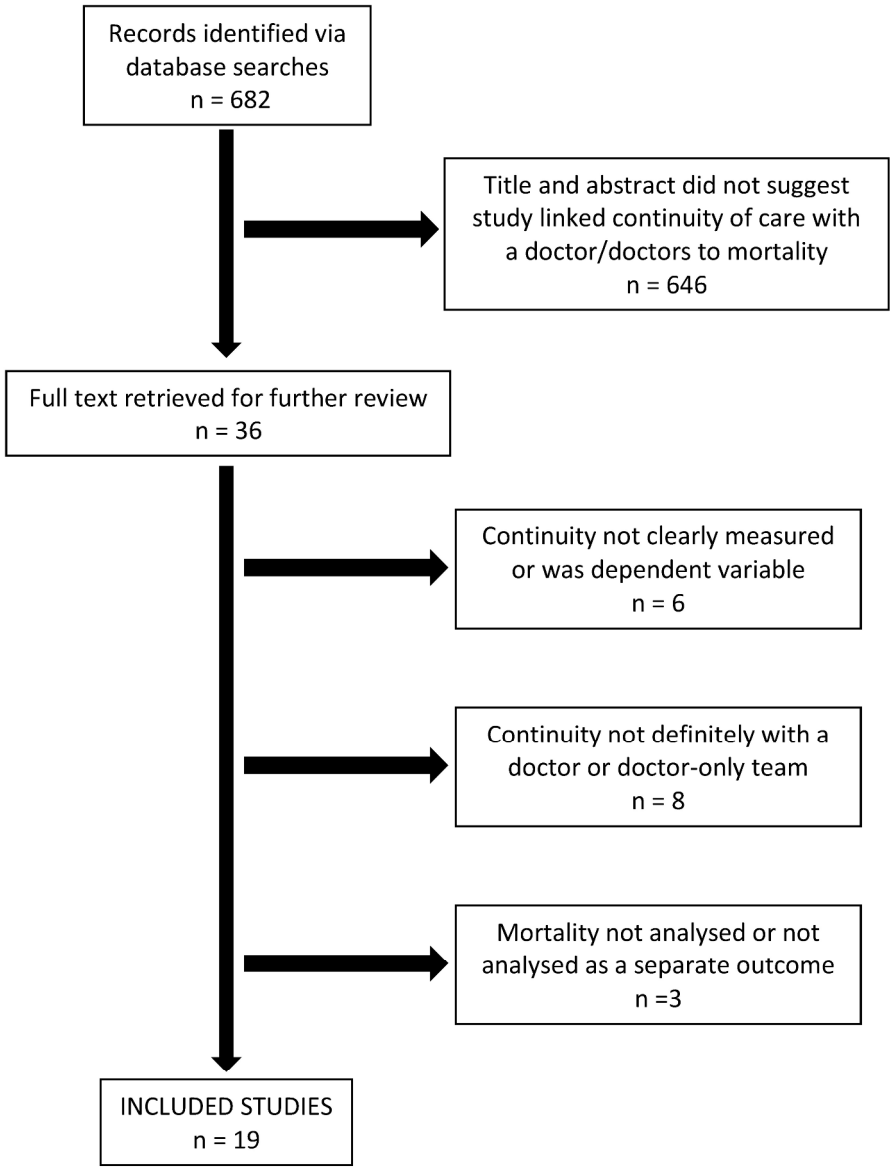

Figure 1. Study selection flow diagram.

171x223mm (600 x 600 DPI)

Supplemental Information

Search terms for Medline search

continuity[Title/Abstract] OR continuity of care[Title/Abstract]

AND

physician[Title/Abstract]) OR doctor[Title/Abstract]) OR general practitioner[Title/Abstract]) OR GP[Title/Abstract]) OR consultant[Title/Abstract]) OR specialist[Title/Abstract]) OR surgeon[Title/Abstract]) OR clinician[Title/Abstract]) OR cardiologist[Title/Abstract]) OR dermatologist[Title/Abstract]) OR gastroenterologist[Title/Abstract]) OR diabetologist[Title/Abstract]) OR geriatrician[Title/Abstract]) OR gerontologist[Title/Abstract]) OR gynecologist[Title/Abstract]) OR gynaecologist[Title/Abstract]) OR hematologist[Title/Abstract]) OR haematologist[Title/Abstract]) OR nephrologist[Title/Abstract]) OR obstetrician[Title/Abstract]) OR oncologist[Title/Abstract]) OR ophthalmologist[Title/Abstract]) OR orthopedist[Title/Abstract]) OR orthopaedist[Title/Abstract]) OR otolaryngologist[Title/Abstract]) OR pediatrician[Title/Abstract]) OR paediatrician[Title/Abstract]) OR psychiatrist[Title/Abstract]) OR pulmonologist[Title/Abstract]) OR hospitalist[Title/Abstract]) OR practitioner[Title/Abstract]) OR physicians[Title/Abstract]) OR doctors[Title/Abstract]) OR GPs[Title/Abstract]) OR Practitioners[Title/Abstract]) OR specialists[Title/Abstract]) OR consultants[Title/Abstract]) OR registrar[Title/Abstract]

AND

death[Title/Abstract]) OR mortality[Title/Abstract]) OR lethality[Title/Abstract]) OR fatality[Title/Abstract]) OR deaths[Title/Abstract]) OR fatalities[Title/Abstract]) OR fatal outcome[Title/Abstract]

Filters

Dates: January 1996-August 2016

English language only

Supplemental Table: Scores for the Newcastle-Ottawa elements. These are the average scores, between two assessors, for each article. Nine is the maximum score possible.

First author and year of publication	Selection	Comparability	Outcome	Total
Baker 2016	3.5	2	2.5	8
Bentler 2014	4	2	3	9
Blecker 2014	3.5	2	2.5	8
Brener 2016	4	2	3	9
Cerovečki 2013	4	1.5	3	8.5
Hoertel 2014	4	1.5	3	8.5
Honeyford 2013	3.5	2	2.5	8
Leleu 2013	4	2	3	9
Levene 2012	4	2	3	9
Liao 2015	4	1.5	3	8.5
Lustman 2015	4	1.5	3	8.5
Maarsingh 2016	4	2	3	9
McAlister 2013	4	2	3	9
Shin 2014	4	2	3	9
Sidhu 2014	4	1.5	3	8.5
Spatz 2014	4	2	3	9
van Walraven 2010	4	2	3	9
Weir 2016	4	1.5	3	8.5
Worral 2011	3.5	0.5	3	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-7 References
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-7, 11 Supplemental
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Continuity of care with doctors- a matter of life and death? A systematic review of continuity of care and mortality.

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Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Health services research
Keywords:	Continuity of Care, Mortality, Systematic review, Doctors, Doctor patient relationship

Continuity of care with doctors- a matter of life and death? A systematic review of continuity of care and mortality.

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Abstract

Objective
Continuity of care is a longstanding feature of health care, especially general practice. It is associated with increased patient satisfaction, increased take-up of health promotion, greater adherence to medical advice and decreased use of hospital services. This review aims to examine whether there is a relationship between the receipt of continuity of doctor care and mortality.

Design
Systematic review without meta-analysis.

Data sources
Medline, Embase and the Web of Science, from 1996 to 2017.

Eligibility criteria for selecting studies
Peer-reviewed primary research articles, published in English which reported measured continuity of care received by patients from any kind of doctor, in any setting, in any country, related to measured mortality of those patients.

Results

Of the 726 articles identified in searches, 22 fulfilled the eligibility criteria. The studies were all cohort or cross-sectional and most adjusted for multiple potential confounding factors. These studies came from nine countries with very different cultures and health systems. We found such heterogeneity of continuity and mortality measurement methods and time frames that it was not possible to combine the results of studies. However, 18 (81.8%) high quality studies reported statistically significant reductions in mortality, with increased continuity of care. 16 of these were with all-cause mortality. Three others showed no association and one demonstrated mixed results. These significant protective effects occurred with both generalist and specialist doctors.

Conclusions

This first systematic review reveals that increased continuity of care by doctors is associated with lower mortality rates. Although all the evidence is observational, patients across cultural boundaries appear to benefit from continuity of care with both generalist and specialist doctors. Many of these articles called for continuity to be given a higher priority in healthcare planning. Despite substantial, successive, technical advances in medicine, interpersonal factors remain important.

Systematic review registration

PROSPERO 2016:CRD42016042091

Strengths and limitations of this study

- The first systematic review of continuity of care and mortality
- We included studies working with patients with all conditions, of all ages and of all stages of conditions.
- We included articles investigating continuity with all kinds of doctor in any health system.
- We included articles using any clearly defined measure of continuity of care.
- A meta-analysis was not possible due to heterogeneity of continuity and mortality measures.

Introduction

Medical science has advanced rapidly since the early nineteenth century. Major advances from the germ theory to the sequencing of the human genome have together generated much deeper understanding of the pathophysiology of disease with improved prevention and treatment. However, all these advances are mostly related to physical factors. Research on human aspects of medical care has lagged.

Internationally, there has been a decrease in the perceived value of personal contact between patients and doctors. An editorial in the New England Journal of Medicine[1] suggested that non-personal care should become the “default option” in medicine.

One way to study interpersonal care is by measuring continuity of care. The definition of continuity of care that we have used previously[2] is repeated contact between an individual patient and a doctor. Such repeated contact gives patients and doctors the opportunity for

improved understanding of each other's views and priorities. Continuity of care can be considered to be a proxy measure for the strength of patient-doctor relationships.[3]

There have been a variety of approaches to measure continuity and so far only three randomised controlled trials have been completed.[4-6] These all showed continuity to be beneficial for patients over relatively short periods. However RCTs are problematic with pre-existing long-term human relationships, like marriage and parent-child relationships, as prospective randomisation is almost impossible. Some doctor-patient relationships last for decades and become highly personal and therefore RCTs are unethical or impractical. Observational studies have inherent limitations and investigating continuity of care has certain problems, in particular that of reverse causality; poor health or death early in the study leading to a low measured level of continuity.[7] However, study teams are increasingly aware of this and use study designs and analytical methods to reduce and account for it.

There is a clear rationale for the effectiveness of continuity of care as doctors collect "accumulated knowledge"[8] about an individual patient which they then use in subsequent consultations to tailor advice.

Continuity of care in general practice is associated with greater patient satisfaction,[9] improved health promotion,[10] increased adherence to medication,[11] and reduced hospital use.[12] Given all these separate benefits the question arises whether these extend to mortality rates. Death is clearly the most important and serious of all outcomes.

Since 2010, individual studies have emerged investigating whether continuity of care is associated with reduced mortality; including some with specialists.[13-35] These reports represent a new development, underlining the interpersonal component of medical care.

Research question

Are higher levels of continuity of doctor care, in any setting, with any patient group, associated with changed mortality?

Methods

Protocol and registration

The protocol for this systematic review was registered on PROSPERO in 2016: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042091

Search strategy and selection criteria

For inclusion in this systematic review (without meta-analysis), articles must have been published in the peer-reviewed literature, in the last 21 years, in English. We searched the databases of *Medline*, *Embase* and the *Web of Science* from 1996 to 2017 by searching for 'continuity' OR 'continuity of care' together with terms for a medical doctor/physician and terms indicating death or mortality in the title or abstract (see supplemental information-example search strategy). In addition, references of articles selected were hand-searched for additional relevant citations.

Experimental and observational study designs were considered including controlled trials, cohort studies (prospective and retrospective) and case-control studies. Systematic reviews and meta-analyses were excluded. Study participants could include any patient group, including entire populations or groups of patients with a specific disease or other feature.

Articles must have compared measured degrees of continuity of care with doctors (of any kind) to mortality rates. Any valid measure of continuity was considered, including continuity being lost or absent and articles where the continuity measure was a single appointment or visit by a general practitioner/family physician during a hospital stay. Articles about organisational continuity and general staffing numbers were excluded.

As an outcome measure, any measure of mortality was accepted, i.e. all-cause, date/age-limited or cause-specific. When complications or hospital admissions were combined with death rates, we sought a separate measure of mortality alone. If this was not available, studies were excluded.

Two pairs of reviewers checked the search results and decided independently whether papers met the eligibility criteria. Initially, the title and abstract of each citation was screened. The full texts of selected articles were then examined. Disagreements were resolved by discussion and PHE independently had the deciding vote.

Data items

The variables and outcomes extracted included basic information: authors, date and country. We also extracted study design, study population (any particular condition, setting, age group, any other inclusion or exclusion criteria and selection method), numbers of patients, measure of continuity, length of continuity measurement and doctor type (generalist doctor including general practitioner, family physician and primary care physician or specialist). We extracted the period of time for the mortality measurement, and any overlap with or interval between mortality and continuity measurement periods. We also extracted whether mortality was all-cause or a disease-specific cause or limited to a particular group, how mortality was assessed and confounding factors tested or accounted for. We also extracted an estimation of any association found, with risk or odds ratios where possible and whether higher continuity was linked to an increased or decreased mortality risk. Data were extracted independently by two reviewers (of DJPG, EW, AT and KSL), using the data extraction table designed for this review. Disagreements were resolved as above.

Risk of bias

The quality and risk of bias was assessed independently for individual studies by two reviewers using the Newcastle-Ottawa Scale[36] We also assessed relevant areas of bias in terms of the timing of continuity and mortality measurement and confounding factors considered. For continuity of care and mortality there is a particular potential for bias in that the worsening of health status before death may cause either decreased or increased continuity of care (reverse causality)[7] so we noted whether this had been considered and adjusted for in study design. In terms of bias across studies, we considered publication bias and reporting bias in terms of whether mortality was the primary outcome.

Data analysis

Studies were analysed for a relationship between continuity of care and mortality rates and whether this relationship was an inverse one (i.e. greater continuity of care led to lower mortality rates) or not. For each study we sought a risk metric (i.e. relative risk, hazard or odds ratio) from an adjusted model of data analysis in order to minimise the risk of selection bias and confounding. Where these statistical metrics were not reported we provided any other available comparison measure.

Patient involvement statement

DJPG is a member of the St Leonard's Practice Patient Participation Group as well as the Patron of the National Association for Patient Participation. As such he is a patient representative as well as an author. The research question and outcomes were therefore conceived by a patient from the practice based on the priorities, experience and preferences stated by patients at successive national patient conferences.

Results

Study selection

After removal of duplicate results, 726 peer-reviewed publications were identified. No previous systematic reviews or trials on this subject were found. Of the 726 papers identified, 43 papers were selected for full text review (Figure 1). Articles were then excluded if continuity was not clearly measured or was the dependent variable[37-42], if the continuity of care measure was not clearly with a doctor or doctors only[35,43-49] and if mortality was not analysed or not analysed separately at any point[50-52] (for example if it was expressed only as a composite outcome with hospitalization). This left 22 studies for inclusion.

Study Characteristics

As shown in Table 1, the majority of included reports (15, 68.2%) were of retrospective cohort studies, often using insurance data. There were four prospective cohort, and three cross-sectional studies. No randomised controlled trials were found. A number of the cohort studies included large numbers of patients (median 16,855). All of the reports were published since 2010. The studies were carried out in nine different countries; the majority were from North America (six-Canada, five-USA). Seven were from Europe (three-England, two- France and one each- Croatia and the Netherlands). There were two from Taiwan and one each from Israel and South Korea.

Nine (40.9%) of the studies investigated continuity with a general practitioner/family physician/primary care physician, three were with specialists only[17,19,20] and ten included continuity with doctors of any kind. Eight studies (34.8%) selected patients during or following an index hospitalization.15-18,20,25,26,29 Five studies studied patients with diabetes[22,23,27,30,31] and three studies focussed on older patients.[13,24,31]

The continuity measures used are reported in Table 1. The most common measure used was the UPC (Usual Provider of Care) index which was used in ten studies

(45.5%).[13,16,17,21,23,25,26,29-31] Six studies used more than one measure, some only for sensitivity analysis.[13,21,25,26,28,29] One study[13] was designed to compare the association of different continuity measures with outcomes, including mortality. One article[18] used the occurrence of a supportive visit by a family physician to a patient in hospital and another[14] simply took loss of contact as meaning loss of continuity. Three studies[32-24] used the results of a question or questions from the annual UK national General Practice Patient Survey (GPPS).

The length of time over which continuity was measured (when not a survey response or hospital visit indicating a relationship) varied greatly between studies, from a single weekend in hospital[17] up to 17 years[24]. The median length of continuity measurement was 2 years (IQR 3.75).

Most studies (20, 90.9%) reported all-cause mortality. One study[32] investigated premature mortality; under the age of 75. Another[33] used premature coronary heart disease mortality as the primary outcome. The length of time for recording deaths also showed a large variation between studies, from 30 days to up to 21 years. The median follow up time was 2.5 years (IQR 4.4).

Most of the studies investigated a large number of potential confounding factors (Table 1). All studies working at the level of individual patients included some measure of health status including LACE index, co-morbidities, previous healthcare usage and other measures. Most studies looked at age and sex and 14 (63.6%) used a measure of deprivation, social status or income.

Table 1. Studies investigating the link between continuity and mortality that meet the inclusion criteria, ordered by study design.

First author and year of publication	Country of origin	Patients	Study design	number of patients if cohort study	Continuity measure	Continuity with	length of time continuity measured	Confounding factors checked and/or adjusted for	Mortality measure	Quality score (Mean(of 2 reviewers)	Mortality primary outcome?	length of time mortality counted
Bentler 2014[13]	USA	65 yrs+ Community residing Medicare beneficiaries who completed NHHSUQ survey, not in managed care, not in MMC plan.	PC	1219	1, 2, 3, 5, 8	Physician	1-2yrs	A,B,C,D,E,F,G,H,I,K,M,N,O	All cause time to death	9	Yes	up to 5 yrs
Cerovečki 2013[14]	Croatia	With opioid dependence, treated with methadone in family medicine setting	PC	287	7	Family physician	12 yrs	A,B,M,O,S	All cause	8.5	Yes	12 yrs
Spatz 2014[15]	USA	18 yrs+, hospitalized with acute myocardial infarction	PC	2454	8	Doctor	N/A	A,B,C,D,E,F,G,I,J,M,O,T	All cause	9	Yes	12 months
van Walraven 2010[16]	Canada	18 yrs+, discharged into community from medical or surgical services of 11 Ontario hospitals	PC	3876	1	Physician who saw patient before, during and/or after hospital stay	6 months	A,B,H,L,N,O	All cause	9	Yes	6 months
Blecker 2014[17]	USA	18 yrs+, hospitalised at least 2 days including at least one at weekend	RC	3391	1	Discharge physician	2 days	A,B,C,K,N,O,T	In hospital	8	No	Length of hospital stay
Brener 2016[18]	Canada	18 yrs+, discharged from hospital into community, family physician has history of hospital visits.	RC	164059	9	Family physician	N/A	A,B,D,L,O,Q	All cause	9	Yes	90 day Post discharge
Hoertel 2014[19]	France	in CNAMTS insurance fund, saw a psychiatrist regularly	RC	14515	2	Psychiatrist	3.5 yrs	A,B,D,K,N,O	All cause	8.5	Yes	3 yrs
Justiniano 2017[20]	USA	18yrs+ underwent colorectal resection and readmitted within 30 days of DC	RC	20016	0	Surgeon	N/A	A,B,C,I,K,O,P,Q,T,U	All cause, colorectal cancer	9	Yes	1 yr
Leleu 2013[21]	France	NHI reimbursement patients, >2 visits in 6 months	RC	325742	1, 2	Primary care physician/GP	3 yrs	A,B,D,K	All cause	9	Yes	3 yrs
Liao 2015[22]	Taiwan	31-99 yrs, with type 2 diabetes	RC	89428	6	Any physician	1 yr	A,B,H,K,N,O,P,U	All cause	8.5	No	4-9 yrs
Lustman 2015[23]	Israel	40-75 yrs, with type 2 diabetes, remained in area, saw primary care provider >3x	RC	23679	1	Primary care physician/GP	2 yrs	A,D,H,K,M,N,O	All cause, diabetes related causes	8.5	Yes	2 yrs
Maarsingh 2016[24]	The Netherlands	55–85 yrs, data available.	RC	1712	3	GP	17 yrs	A,B,D,E,F,G,K,M,Q,O	All cause	9	Yes	21 yrs
McAlister 2013[25]	Canada	20 yrs+ DC from hospital with 1st time heart failure	RC	16855	0, 1	Physician who saw patient x2 in yr before or 1x during admission	N/A	D,K,O,P,Q,R	All cause	9	Composite	3m/6m
McAlister 2016[26]	Canada	20 yrs+ DC from hospital with 1st time heart failure	RC	39249	0,1	Any physician	N/A	A,B,Q,K,M,O,H	All cause	8	Composite	30 days
Pan 2017[27]	Taiwan	35 yrs+, diagnosed with type 2 diabetes, in Taiwan NHI database.	RC	396838	2	Any physician	8 years	A,B,D,K,O,P,Q	All cause	8.5	Yes	up to 8 years

Shin 2014[28]	South Korea	20 yrs+, in Korean National Health Insurance, new diagnosis of hypertension, diabetes, hypercholesterolemia or their complications.	RC	47433	2, 4, 5	Physician	2 yrs	A,B,D,F,K,N, Q,U	All cause	9	Yes	up to 5 yrs
Sidhu 2014[29]	Canada	"Adults" treated and released from 93 Emergency departments with first time diagnosis of Heart Failure	RC	12285	0, 1	Physician who saw patient x2 in year before or 1x during admission	30 days	A,B,G,K,O,P, Q,N	All cause	8.5	Composite	12months but only give separate data for deaths for 30 days
Weir 2016[30]	USA	20 yrs+, with incident diabetes and at least 2 years insurance.	RC	285231	1	physician who saw patient the most	2 yrs	A,B,D,G,H,K, O	All cause	8.5	Composite	1 yr
Worrall 2011[31]	Canada	65 yrs+, with diabetes, 2+ fee-for-service family physician visits.	RC	305	1	Family physician	3 yrs	A,B,N	All cause	7	Yes	3 yrs
Baker 2016[32]	England	Registered with 7858 general practices, with complete data, in England	CS	N/A	8	GP	N/A	C,D,F,G,J,P	premature- ratio observed to expected, age < 75	8	Yes	N/A
Honeyford 2013[33]	England	Registered with 229 general practices in the east Midlands between April 2006 and March 2009	CS	N/A	8	GP	N/A	A,B,C,D,F,G,P ,U	CHD under 75 and all age	8	Yes	3 yrs
Levene 2012[34]	England	18 yrs+, registered with GP for at least 6/12 months of the year	CS	N/A	8	GP	N/A	A,B,C,D,F,O,P	All cause, COPD, all cancer, CHD	9	Yes	2 yrs

Key

Abbreviations for types of study-PC= Prospective Cohort, RC= Retrospective Cohort, CS=Cross-Sectional

Continuity measures		F	Smoking
1	Usual provider of care index	G	Chronic conditions
2	Continuity of care index	H	Prior hospitalisation
3	Herfindahl-Hirschmann index	I	Insurance
4	Modified, modified continuity Index	J	Acute conditions
5	Most frequent provider	K	Co-morbidity (including Charlston index)
6	% consistency to physician	L	LACE index (risk of 30 day re-admission or death after hospital discharge)
7	Loss of contact with family physician	M	Marital/ relationship status
8	Patient survey	N	Number of healthcare visits/service intensity
9	Family physician visited patient in hospital	O	Other healthcare history
0	Follow up by familiar doctor	P	Practice, hospital or doctor characteristics
Confounding factors		Q	Location
A	Age	R	Length of hospital stay
B	Sex	S	Treatment plan
C	Race	T	Timing of admission
D	Deprivation/social status/income	U	Other
E	Education		

Results of individual studies

Of the 22 studies, 18 (81.8%) showed that greater of continuity of care was significantly associated with lower mortality. Of these, 16 (72.7% of the 22) were with lower all-cause mortality (Table 2). Two studies found no association of greater continuity of care with subsequent mortality during[17] or following[16] a hospital stay. One study found that continuity was not significantly associated with mortality except in general practices in the least deprived areas.[32] One study[13] investigated a range of continuity measures. They found that all insurance claims-based measures showed that higher levels of continuity were associated with higher mortality rates but greater continuity as reported by patients was associated with reduced mortality. This is the only study showing any association of increased continuity with increased mortality.

Due to the heterogeneity of study continuity and mortality measurements, it was not possible to combine them to produce an estimate of effect size however Table 2 shows the risk, odds or hazard ratios from individual studies where available.

Table 2. Outcome measures of studies investigating the association of continuity of care with mortality

First author and year of publication	Ratio (if available)	Other result	95% CI	for measure	Continuity associated with mortality?	Results summary
Bentler 2014[13]	2.25†		1.33-3.81	AHR above vs below mean patient-reported care site continuity	Yes	Patient-reported duration continuity had significant, protective association with time to death. Seven claims-based continuity of care indicators and one patient-reported measure (Site continuity) showed higher continuity associated with increased death hazard
	0.54*		0.37-0.8	AHR, highest v lowest tertile patient-reported duration continuity		
	2.3†		1.56-3.38	AHR,highest v lowest tertile, UPC		
	1.8†		1.12-2.88	AHR,highest v lowest tertile, Inverse number of providers		
	1.69†		1.13-2.52	AHR,highest v lowest tertile, MMCI		
	1.7†		1.12-2.59	AHR,highest v lowest tertile, Ejlertsson's index K		
	2.33†		1.56-3.49	AHR,highest v lowest tertile, Bice Boxerman CoC		
	1.98†		1.23-3.21	AHR,highest v lowest tertile, MCI		
	2.35†		1.59-3.49	AHR,highest v lowest tertile,sequential continuity		
Cerovečki 2013[14]	12.6*		3.001-53.253	OR, loss of COC	Yes	Loss of continuity of care one predictor of fatal outcome.
Spatz 2014[15]	1.92*		1.19-3.12	AHR, No usual source of care vs strong usual source of care (USOC) relationship	Yes	In multivariable analysis, having no USOC associated with higher 12-month mortality
van Walraven 2010[16]	1.03		0.95-1.12	AHR, increase of 0.1 in continuity score, preadmission physician	No	No significant association found for death risk with continuity with any doctor type studied
	0.87		0.74-1.02	AHR, increase of 0.1 in continuity score, hospital physician		
	0.97		0.89-1.06	AHR, increase of 0.1 in continuity score, post-discharge physician		
Blecker 2014[17]	0.72		0.29-1.8	AOR, UPC 1 (complete continuity) vs 0, no continuity	No	Increased weekend UPC was significantly associated with decreased mortality in unadjusted analysis. No association after multivariate adjustment.
Brener 2016[18]	0.87*		0.82-0.93	AOR, visited vs not, 90 day post discharge	Yes	In unadjusted model, visited patients more likely to die at 90 days. In unadjusted model, visited patients less likely to die at 90 days
	0.88*		0.81-0.86	AOR, visited vs not, 30 day post discharge		
Hoertel 2014[19]	0.83*		0.83-0.83	AHR, 0.1% increase in COC index	Yes	0.1 increase in COC index associated with decreased likelihood of death.
	0.53*		0.52-0.54	AHR, perfect continuity vs imperfect continuity		
Justiniano 2017[20]	2.33		2.10-2.60	AHR, readmitted to original hospital but with different surgeon vs same hospital, same surgeon.	Yes	In comparison with patients readmitted to the same hospital and managed by the same surgeon, patients managed at the same hospital but by a different surgeon had an over 2-fold risk of 1-year mortality
Leleu 2013[21]	0.96*		0.95-0.96	HR, 0.1 increase in COC	Yes	Increase in the COC index associated with decrease in death risk
Liao 2015[22]	*	Significant trend (P<0.001, test for monotonic trend)		decreasing consistency in medical care seeking behaviour with decreasing adjusted survival	Yes	A significant monotonic trend was observed between decreasing consistency in medical care–seeking behaviour (from high consistency to low consistency) and decreasing multivariate-adjusted survival
Lustman	0.59*		0.5-0.7	OR, high vs low UPC, measured at same time	Yes	Patients with a high UPC had lower risk of mortality. Not

2015[23]	0.7*		0.56-0.88	OR, high vs low UPC, measured in successive years		affected on adjusting for background characteristics.
Maarsingh 2016[24]	1.2*		1.01-1.42	HR, lowest vs highest COC	Yes	In final model, participants in lowest COC category showed greater mortality than those in maximum.
McAlister 2013[25]	0.86			HR, familiar vs unfamiliar (our calculation, CI not available)	Yes	After 6 months death HR for familiar Dr 0.66 (95%CI 0.61-0.71) and 0.77 (0.68-0.88) with unfamiliar vs no follow up. At 3 months 1.6% of those who had a visit with a familiar Dr died, 3.3% who only saw an unfamiliar Dr, P<0.001
McAlister 2016[26]	*	3.1% vs 2.0% P<0.0001		% mortality- follow up by unfamiliar or familiar physician	Yes	More died with follow up with unfamiliar physician compared with those with at least one visit with familiar physician.
Pan 2017[27]	0.47*		0.46-0.48	AHR high (>50%) vs low (≤50%) COCI score	Yes	Patients with diabetes with higher physician continuity had a lower risk of mortality.
Shin 2014[28]	1.13*		1.05-1.21	AHR, below vs above median most frequent provider	Yes	Above median continuity associated with lower all-cause mortality using 3 different measures
	1.13*		1.05-1.21	AHR, below v above median MMCI		
	1.12*		1.04-1.21	AHR, below v above median COC		
Sidhu 2014[29]	*	1.9% vs 1.4% P<0.0001		% mortality- follow up by unfamiliar or familiar physician	Yes	More died with follow up with unfamiliar physician compared with those with at least one visit with familiar physician.
Weir 2016[30]	0.75*		0.61-0.94	AOR, high v low UPC	Yes	High UPC associated with decreased mortality
Worral 2011[31]	*	9.0% vs 18.1% (P=0.025, χ^2)		% mortality-high vs low continuity group.	Yes	Proportion of people dying significantly lower in high-continuity group
Baker 2016[32]		21 deaths	−16 to 63	Potential reduction in premature deaths in England in 1 year if there is a change of 1 percentile of patients expressing trust in their doctor	No	Continuity not associated with mortality (except in less deprived practices in a separate subgroup analysis).
		-49 deaths	−250 to 156	Potential reduction in premature deaths in England in 1 year if there is a change of 1 percentile of patients able to get an appointment in advance		
Honeyford 2013[33]	0.994*		0.989-1	IRR,1% change in survey response	Yes	An increase in % of patients recalling being able to see their preferred GP was associated with decreased mortality
Levene 2012[34]	0.999		0.997-1.01	IRR, All-cause mortality	Depends on mortality measure	No significant association with all-cause mortality. An increase in the % of patients recalling being better able to see their preferred doctor was associated with decreases in COPD mortality and in all cancer mortality.
	0.997*		0.995-0.999	IRR, All cancer mortality		
	0.999		0.995-1.07	IRR, Coronary Heart Disease mortality		
	1.0002		0.99-1.01	IRR, Stroke mortality		
	0.993*		0.98-0.998	IRR, COPD mortality		

Key
* Significant result showing higher levels of continuity associated with lower mortality
† Significant result showing higher levels of continuity associated with higher mortality

Abbreviations
HR- Hazard ratio
OR- odds ratio
AHR- adjusted hazard ratio
AOR- adjusted odds ratio
IRR- incident rate ratio
UPC- usual provider of care index
COC- continuity of care index

Risk of bias within studies

Using the Newcastle-Ottowa scale,[36] all 22 studies were rated as high quality, with 9 ten studies (40.9%) gaining maximum scores from both reviewers independently (Table 1, Supplemental Table). No study was scored less than 7 out of 9 by any reviewer. As all these studies were cohort or cross-sectional studies, they tested for associations only. However, most involved statistical analyses for a wide range of potential confounding factors (Table 1).

The specific bias of reverse causality between the healthcare-related events that might occur before death was discussed in 14 (63.6%) of the studies. Four cohort studies did not discuss reverse causality.[14,24,27,31] However, all of the studies included some measure of health/disease status as a potential confounding factor and some included several detailed measures of these in their models.

Five of the studies had a design which meant there was no overlap between the time for continuity measurement and the period during which deaths were counted.[13,20,22,28,30] Seven studies have complete[14,1621,23,28,29,31] and four partial overlap of these periods.[17,19,24,25] five studies included additional analyses which either eliminated the overlap[23] or introduced a lag time[19,21,26,28] between continuity and mortality measurement periods. In each of these additional analyses, continuity was still found to be significantly associated with mortality. One long term study[24] calculated survival from the date of the last continuity measurement and stratified by the length of time in the study. Five studies[19,21,25,28,29] used their continuity score as a time dependent variable in the model.

Risk of bias across studies

There is a risk of publication bias. It may be that reports showing no effect are less likely to be published. However, two showed no association. In two, mortality was not the primary outcome and in six, it was part of a composite outcome. For 13 studies, mortality was not the only outcome. In ten studies the association of two or more factors, including doctor continuity of care, with outcomes was tested. Continuity and mortality as exposure and outcome respectively, are reported in a range of studies, including where testing this association was not the primary aim.

Discussion

Principal Findings

In a substantial majority of studies (18, 81.8%) meeting the selection criteria, higher levels of continuity of care with doctors were associated with lower mortality rates. Two others, finding no significant association, had very short timescales for measurement of continuity, to the extent that the strength of any patient-doctor relationship was potentially questionable. Another study showing no significant association with all-cause mortality was cross-sectional and the measurement methods related to questions on a national survey about seeing a particular general practitioner, again not necessarily indicative of a strong patient-doctor relationship.

One study[8] found that for claims-based measures of continuity, increased mortality was associated with higher levels of continuity of care. However in the same study, higher levels of patient-reported continuity were associated with lower mortality rates. This emphasises the interpersonal relationship between patient and doctor as claims-based measures only give numbers of contacts and do not directly measure the quality of the relationship.

The effect sizes were generally small (Table 2) but these were in the same range as some treatment effects, as very large, repeatable effects on mortality are rare.[53] In addition, for some studies included in this review, effect sizes were calculated using very small increments in the continuity measure.

Strengths and weaknesses of the evidence

All the studies found investigating the association of continuity of care with mortality were observational in nature, although the majority are high quality cohort studies including three prospective cohort studies. The issue of reverse causality applies to all the evidence presented here. This could bias an association between continuity of care and mortality in either direction. As patient health worsens when approaching death, continuity of care may deteriorate for many reasons e.g. patients moving areas to accommodate increased health needs, the need to see more specialists, or a loss of ability to obtain and attend appointments. Alternatively, deterioration of health could lead to a concerned doctor ensuring that the patient receives more continuity of care. For the cross-sectional studies there is also potential for confounding due to practice-level factors.

There have been randomised controlled trials into continuity of care but none on existing relationships or lasting longer than a year and none with mortality as an outcome.[4-6] Observational studies which control rigorously for confounding factors and have a design aimed at limiting the impact of reverse causality are the best evidence available.

Of the 16 cohort studies finding an association of higher continuity with lower mortality, most studies attempt to at least partially account or control for reverse causality in their study design or analysis. Most controlled for differences in health status and risk factors. Some carried out analyses measuring continuity and mortality in separate years, or with a lag. This method, particularly the lag between measurements, should help to minimise bias

caused by rapid worsening prior to death. However, four cohort studies showing this association[14,24,27,31] did not discuss this kind of reverse causality although one[24] nevertheless made several adjustments for health status and calculated survival from the date of the last continuity measurement. Measuring continuity and mortality over separate time periods is also one way of eliminating the potential bias caused by those who survived longer having more time to accrue continuity (time-dependent bias). Another way of reducing this is to model continuity as a time-dependent variable which was the case in five studies.[19,21,25,28,29]

All studies included were rated as high quality, using the Newcastle-Ottawa scale.
Several of the articles reported on studies using very large cohorts. The studies came from a number of different countries with different healthcare systems and cultures. Continuity of care in the studies included that received from specialist as well as generalist doctors, showing that the effect is not limited to one branch of medicine or health system.

As continuity research is an emerging field, no consensus on the best way to measure it has been reached. The measure used most was the UPC index which does not take into account the total number, frequency or sequence of visits.[54]

Doctors have been studied as a discrete category in numerous studies and data systems usually allow them to be separately studied. The group studied included family doctors/general practitioners, physicians and psychiatrists so was already heterogeneous so expanding this to other professional groups would have complicated interpretation. As doctors are the most highly-trained health professionals with the most influence over decisions, it is reasonable to assume that if interpersonal contact affects mortality, it is most likely to occur with doctors. Therefore we eliminated articles, some with significant reductions in mortality, that measured continuity in relation to mixed profession teams or to other health professionals.[35,43-49] This is the first systematic review investigating whether continuity of doctor care is associated with reduced mortality. We expect this to encourage studies with different selection criteria; for example for continuity with other healthcare professionals.

Possible mechanisms and implications

This review, finding that increased receipt of continuity of care is associated with reduced mortality comes after it has been shown that continuity of care is associated with multiple benefits for patients.[9-12] It therefore fits well with such earlier work. It is only recently that large databases and long-term cohort studies have made effective investigation into links between continuity and mortality possible.

These known associations suggest possible mechanisms in that greater uptake of evidence-based preventative medicine such as immunisations as well as better concordance with treatments are likely to reduce mortality. Continuity of care is associated with patients perceiving that the doctor has become more responsive.[55] Patients then disclose more and medical management is more likely to be tailored to the needs of the patient as a person. The increased patient satisfaction may also be associated with an “optimism” boost to health.[56] We have previously suggested that “doctors tend to overestimate their

effectiveness when consulting with patients they do not know, and underestimate their effectiveness when consulting with patients they know."[57]

The cumulative impact of these multiple gains may then be reflected in reduced mortality. Historically continuity of care has been considered a feature of the practice of medical generalists and featured in the job descriptions of the general practitioner.[58,59] Recent studies included in this review found that continuity is associated with reduced mortality with specialist physicians, [22,28] , psychiatrists[19] and surgeons[20]too.

Although this evidence is observational, with 18 of the 22 studies showing significant reductions in mortality with continuity of doctor care, the clear preponderance of evidence is in favour of the association. Three studies show no significant association and one[13] had mixed results but no study exclusively showed an association of higher continuity of care with higher mortality rates. Although there are difficulties in carrying out controlled trials on this subject, a few, with interventions to increase continuity of care, have been successful[4-6] and this could be attempted more widely. The presence of this association in nine countries, across three continents, and in very different populations and health care systems implies a basic human effect.[60] The policy implication as many studies noted is prioritising continuity of care.

For 200 years, medical advances have been mainly technical and impersonal, which has reduced attention to the human side of medicine. This systematic review reveals that despite numerous technical advances, continuity of care is an important feature of medical practice, and potentially a matter of life and death.

Contributors

DJPG conceived the idea for the systematic review. KS-L wrote the protocol with input from other authors and submitted it to PROSPERO. AT, EW and KS-L carried out database searches. DJPG, KS-L, AT and EW carried out article selection, data extraction and assessing article quality. PHE had the deciding vote in article selection, data extraction and assessing article quality. KS-L carried out data analysis. All authors wrote and edited the manuscript. All authors approved the manuscript for publication.

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Transparency statement

DPG is guarantor of the paper and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Data sharing statement

No additional unpublished data available.

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Declaration of interests

All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Figure legend:

Figure 1. Study selection flow diagram.

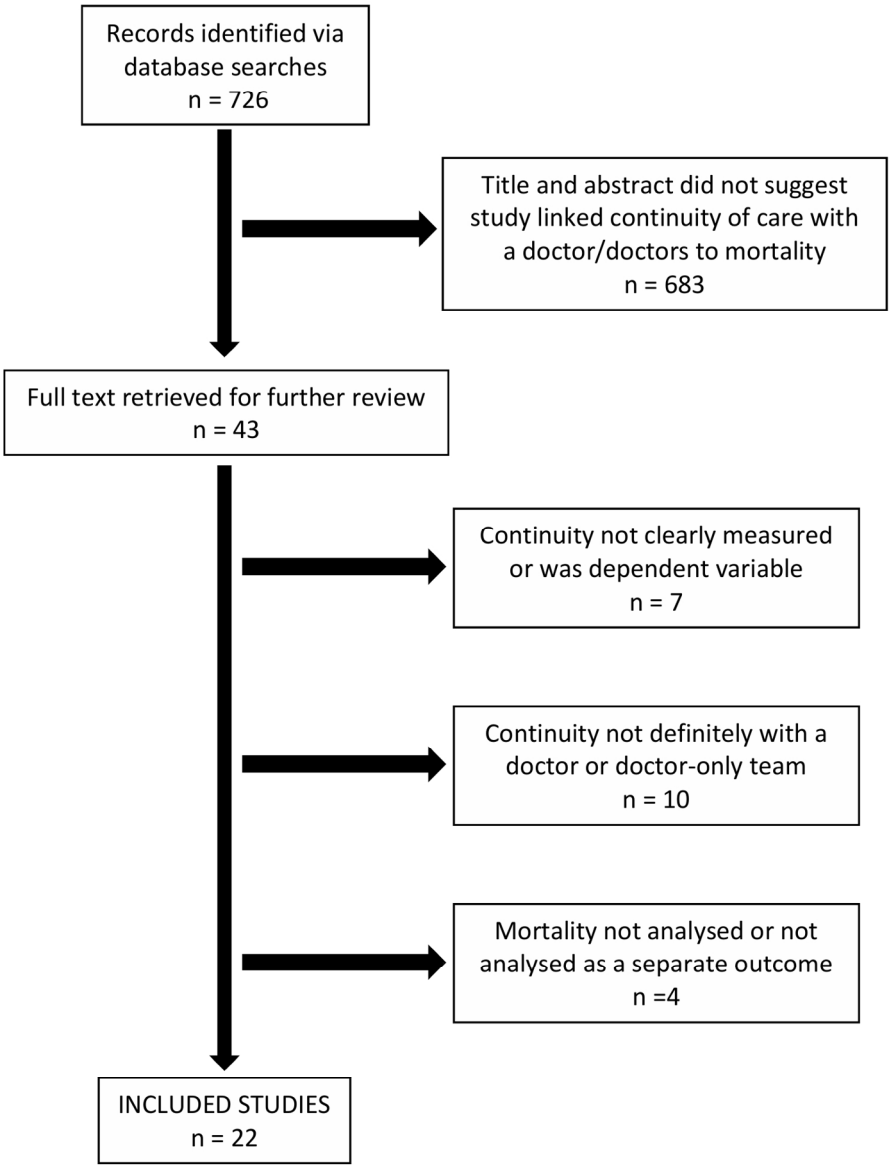

Figure 1. Study selection flow diagram

132x171mm (300 x 300 DPI)

Supplemental Information

Search terms for Medline search

continuity[Title/Abstract] OR continuity of care[Title/Abstract]

AND

physician[Title/Abstract]) OR doctor[Title/Abstract]) OR general practitioner[Title/Abstract]) OR GP[Title/Abstract]) OR consultant[Title/Abstract]) OR specialist[Title/Abstract]) OR surgeon[Title/Abstract]) OR clinician[Title/Abstract]) OR cardiologist[Title/Abstract]) OR dermatologist[Title/Abstract]) OR gastroenterologist[Title/Abstract]) OR diabetologist[Title/Abstract]) OR geriatrician[Title/Abstract]) OR gerontologist[Title/Abstract]) OR gynecologist[Title/Abstract]) OR gynaecologist[Title/Abstract]) OR hematologist[Title/Abstract]) OR haematologist[Title/Abstract]) OR nephrologist[Title/Abstract]) OR obstetrician[Title/Abstract]) OR oncologist[Title/Abstract]) OR ophthalmologist[Title/Abstract]) OR orthopedist[Title/Abstract]) OR orthopaedist[Title/Abstract]) OR otolaryngologist[Title/Abstract]) OR pediatrician[Title/Abstract]) OR paediatrician[Title/Abstract]) OR psychiatrist[Title/Abstract]) OR pulmonologist[Title/Abstract]) OR hospitalist[Title/Abstract]) OR practitioner[Title/Abstract]) OR physicians[Title/Abstract]) OR doctors[Title/Abstract]) OR GPs[Title/Abstract]) OR Practitioners[Title/Abstract]) OR specialists[Title/Abstract]) OR consultants[Title/Abstract]) OR registrar[Title/Abstract]

AND

death[Title/Abstract]) OR mortality[Title/Abstract]) OR lethality[Title/Abstract]) OR fatality[Title/Abstract]) OR deaths[Title/Abstract]) OR fatalities[Title/Abstract]) OR fatal outcome[Title/Abstract]

Filters

Dates: January 1996-December 2017

English language only

Supplemental Table: Scores for the Newcastle-Ottawa elements. These are the average scores, between two assessors, for each article. Nine is the maximum score possible.

First author and year of publication	Selection	Comparability	Outcome	Total
Bentler 2014	4	2	3	9
Cerovečki 2013	4	1.5	3	8.5
Spatz 2014	4	2	3	9
van Walraven 2010	4	2	3	9
Blecker 2014	3.5	2	2.5	8
Brener 2016	4	2	3	9
Hoertel 2014	4	1.5	3	8.5
Justiniano 2017	4	2	3	9
Leleu 2013	4	2	3	9
Liao 2015	4	1.5	3	8.5
Lustman 2015	4	1.5	3	8.5
Maarsingh 2016	4	2	3	9
McAlister 2013	4	2	3	9
McAlister 2016	4	2	2	8
Pan 2017	4	1.5	3	8.5
Shin 2014	4	2	3	9
Sidhu 2014	4	1.5	3	8.5
Weir 2016	4	1.5	3	8.5
Worral 2011	3.5	0.5	3	7
Baker 2016	3.5	2	2.5	8
Honeyford 2013	3.5	2	2.5	8
Levene 2012	4	2	3	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8 References
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8, 12 Supplemental
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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