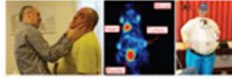




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Scoping review of the impact of multi-morbidity on quality of healthcare: implications for health policy, research and clinical practice.

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ABSTRACT

The simultaneous presence of multiple conditions in one patient (multimorbidity) is a key challenge facing healthcare systems globally. It potentially threatens the coordination, continuity and safety of care. In this paper, we report the results of a scoping review examining the impact of multi-morbidity on the quality of healthcare. We used its results as a basis for a discussion of the challenges that research in this area is currently facing. In addition, we discuss its implications for health policy and clinical practice.

The review identified 37 studies focussing on multi-morbidity but using conceptually different approaches. Studies focusing on 'co-morbidity' (i.e. the 'index disease' approach) suggested that quality may be enhanced in the presence of synergistic conditions, and impaired by antagonistic or neutral conditions. Studies on 'multi-morbidity' (i.e. multiplicity of problems) and 'morbidity burden' (i.e. the total severity of conditions) suggested that increasing number of conditions and severity may be associated with better quality of healthcare when measured by process or intermediate outcome indicators, but with worse quality when patient-centred measures are used.

However, issues related to the conceptualisation and measurement of multi-morbidity (inconsistent across studies) and of healthcare quality (restricted to evaluations for each separate condition without incorporating considerations about multi-morbidity itself and its implications for management) compromised the generalizability of these observations. Until these issues are addressed and robust evidence becomes available, clinicians should apply minimally invasive and patient-centred medicine when delivering care for clinically complex patients. Health systems should focus on enhancing primary care centred coordination and continuity of care.

KEY MESSAGES

- Patients with multi-morbidity might be at a higher risk of receiving poor healthcare, but strong empirical evidence is lacking.
- Clinicians should apply minimally invasive and patient-centred medicine when delivering care for clinically complex patients.
- Health systems should enhance primary care centred coordination and continuity of care.

KEYWORDS: multi-morbidity, comorbidity, health services needs and demand, quality of health care, primary care, scoping review

INTRODUCTION

The increasing prevalence of long-term conditions is the main challenge facing healthcare systems globally (1). Patients with multiple health conditions, known as multi-morbidity (2), constitute a significant proportion of patients in primary care (3). Multi-morbidity presents an increasing tension between desired healthcare models that are truly centred around the patient and current health services, which are usually organized around the diagnosis and management of individual health conditions (4). This tension has the potential to be particularly detrimental to patients with higher degrees of multi-morbidity, who may receive poor quality of healthcare. People suffering from multiple health conditions are more likely to require an increased number of healthcare processes, which will also trigger the involvement of an increased number of health professionals (5). This increased complexity in the delivery of healthcare may threaten coordination, continuity and safety, thereby decreasing the likelihood of receiving care that meets high standards for quality (6, 7). The high prevalence of polypharmacy with aging may lead to an increased risk of inappropriate drug use, under-use of effective treatments, medication errors, poor adherence, drug–drug and drug–disease interactions and, most importantly, adverse drug reactions (8).

Alternatively, it may be also argued that the increased interaction with the health services might result in increased opportunities for receiving effective care (9). The presence of synergistic morbidities (i.e., those representing parts of the same overall pathophysiologic risk profile and therefore more likely to be the focus of the same disease and self-management plan) may also provide increased incentives for both patients and

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3 professionals for adhering to guidelines for recommended care (10). It is possible, however,
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5 that both the described threats and benefits operate simultaneously. Therefore, in order to
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7 increase our understanding in this area, evidence from empirical studies is much needed.
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10 However, research in this complex area is facing a number of important challenges that
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12 limits its progression.
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15 In this article we present the results of a scoping review to “map” existing empirical
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17 evidence on the impact of multi-morbidity on quality in primary care. Subsequently, we use
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19 that information to discuss the limitations and challenges that research in this field is
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21 currently facing. Finally, we discuss its implications for health policy, research and clinical
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23 practice.
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METHODS

A detailed description of the methodology used for the scoping literature review is available in Box 1. Scoping reviews have been defined as “a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge” (11). We selected a scoping (rather than a systematic) literature review approach because (a) the impact of multi-morbidity on quality of healthcare constitutes an emerging research field, and (b) scoping reviews have been identified as a more suitable method to inform practice, policymaking, and research (11).

We searched Medline for studies published from inception to February 2015 (search strategy available in the online supplemental table 1). We included studies containing empirical research examining the quality of healthcare provided to patients with multi-morbidity in the context of primary care.

In accordance to the framework proposed by Valderas et al. (2), four separate multi-morbidity constructs were taken into account: multi-morbidity (“the presence of more than one distinct condition in an individual”(2)), co-morbidity (“any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study”(12)), morbidity burden (“overall impact of the different diseases in an individual taking into account their severity”(13)), and clinical complexity (“the overall impact of the different diseases in an individual taking into account their severity and other health-related attributes”(14)).

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3 Quality of healthcare was conceptualized according to the definition proposed by Campbell
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5 et al.: “whether individuals can access the health structures and processes of care which
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7 they need and whether the care received is effective” (15).
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RESULTS

Results of the literature review are outlined in Box 2. All 37 empirical studies identified (16-52) were published during the previous decade, and had been mostly conducted in the United States. The studies included measures of multi-morbidity, co-morbidity and/or morbidity burden, but none measured patient complexity. The vast majority of the studies measured quality of healthcare based on either condition-specific indicators of healthcare processes (e.g., percentage of patients with diabetes with a record of retinal screening during the last 12 months; percentage of patients with heart failure that were offered anticoagulation therapy, etc.) and/or intermediate outcomes (e.g., percentage of patients with diabetes whose last measure of glycated haemoglobin was $\leq 7.5\%$; percentage of patients with hypertension whose last blood pressure reading was $\leq 140/80$ mm Hg, etc.), or on patient-reported information on patient-centred care (e.g., patients' ratings of patient-provider communication; patient experiences of relational and management continuity, etc.).

Multi-morbidity

In the ten studies specifically examining the impact of multi-morbidity on quality of healthcare (table 1)(23, 24, 27, 29, 30, 33, 41, 43-45), the approach used to measure multi-morbidity varied substantially both in terms of the type of long-term conditions examined and the methods used to group patients according to number of conditions.

Studies consistently observed that multi-morbidity had an impact on the quality of healthcare, but the nature of the impact (positive or negative association) seemed to be

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2
3 dependent on the methodology used to measure quality of healthcare. All six studies that
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5 focused on process or outcomes indicators (27, 29, 41, 43-45) observed a positive
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7 association between multi-morbidity and quality and safety (i.e., patients with multi-
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9 morbidity received higher quality and safety of healthcare than patients with no or only one
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11 condition), whereas all four studies using patient-reported information of quality of
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13 healthcare (23, 24, 30, 33) observed a negative association.
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16 17 18 *Morbidity burden* 19

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21 Out of the four studies identified examining the impact of morbidity burden on quality of
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23 healthcare (18, 25, 40, 41) (table 2), just one study focused on patient reported experiences,
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25 observing worst quality of healthcare among patients with higher levels of morbidity burden
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27 (18). All of the remaining three studies used quality indicators of processes of care and/or
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29 intermediate outcomes and observed a positive association between morbidity burden and
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31 quality of healthcare (40, 41), except for one study (25).
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34 35 36 *Co-morbidity* 37

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39 The vast majority of studies (n=24; 65%) actually focused on the additional impact that
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41 comorbid conditions had on the healthcare for an index condition (16, 17, 19-22, 26, 28, 31,
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43 32, 34-39, 42, 46-52) (table 3). The index condition most frequently examined was diabetes
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45 (nine studies); followed by hypertension and depression (three studies each). Ten of the
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47 studies restricted their analysis to the number of comorbidities or the degree of burden,
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49 whereas the rest of them examined the specific impact of each comorbidity or group of
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51 comorbidities (synergistic and antagonistic) on quality of healthcare.
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3 In general, the results suggested that quality of healthcare measured by condition specific
4 indicators might be enhanced in the presence of synergistic combinations of conditions, and
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6 possibly impaired by the presence of antagonistic conditions (i.e., those not directly related
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8 in either their pathogenesis or management). This pattern was especially apparent for those
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10 studies examining quality of healthcare provided to patients with diabetes; a fact that
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12 supports the framework proposed by Piet et al. (53) on the impact of comorbidity for
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14 diabetes care, but that would be in principle applicable to many other index conditions.
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DISCUSSION

Current challenges in research on quality of healthcare for patients with multi-morbidity

Although some patterns seem to emerge from our review, a word of caution is needed before embracing the available evidence, as there are important issues related to the measurement of both multi-morbidity and quality of healthcare that compromise the generalization of these studies.

Definition and measurement of multi-morbidity First, there is a lack of consistency not only in the selection of the construct for characterizing clinical complexity (multi-morbidity, co-morbidity, and morbidity burden) (54), but also in the very definition of each of them, impairing our ability to pool results across studies. There are very good reasons why researchers and policy makers may want to focus specifically on selected groups of patients with multi-morbidity, such as those with chronic conditions, those with conditions considered unrelated, or those with a particularly high number of concurrent conditions (three or more, sometimes four or more conditions). It makes little sense, however, to constantly redefine multi-morbidity so that it incorporates specifications such as those listed above, which should be used to further characterize multi-morbidity, instead of used to define its boundaries. The very same is applicable to co-morbidity as a specification of multi-morbidity.

Defining the populations of interest is therefore one of the key challenges for advancing research and improving care for patient with multi-morbidity and there is little doubt that a

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3 focus on the most prevalent chronic conditions, and on the different combinations (clusters)
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5 that underlay the emergence of multi-morbidity, is clearly a priority (55).
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9 *Definition and measurement of quality healthcare for multi-morbidity* Secondly, but also
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11 crucial to progress in our understanding of this research area, is establishing what
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13 constitutes quality healthcare for patients with multi-morbidity. There is no doubt that
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15 quality for patients with multi-morbidity must take into account the evidence for the
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17 management of each individual condition. High quality healthcare for a patient with
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19 hypertension, osteoarthritis and chronic obstructive pulmonary disease must be informed
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21 by best practice guidelines for each of these three conditions. However, it is *also* essential to
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23 incorporate considerations about multi-morbidity itself and its implications for
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25 management. We can hardly speak of high quality of healthcare for patients with multi-
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27 morbidity if the potentially antagonistic goals are not adequately addressed, interactions
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29 between the corresponding medications are not carefully examined, and adequate
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31 coordination does not ensure smooth follow up and monitoring of each of the conditions,
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33 while at the same time avoiding overexposing the patient to unnecessary healthcare. And
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35 yet all these issues have been grossly overlooked, restricting evaluations to the specifics of
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37 care for each separate condition and considering the evaluation of care as a whole the same
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39 as the sum of discrete evaluations of care for each condition.
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47 We still lack thoroughly validated and well-established indicators that are fit for this
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49 purpose, as it is still unclear what constitutes good or poor healthcare when we think in
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51 terms of patients with multi-morbidity. Quality of healthcare is defined in relation to
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53 standards, and the key issue here is that we lack clear standards for patients with multi-
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55 morbidity. The applicability of current evidence-based guidelines to multi-morbid patients is
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3 limited (56), and can be problematic (57). Not providing guideline-consistent care for people
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5 with multi-morbidity cannot necessarily be equated with poor quality of care (an
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7 assumption made in all previous studies), as this may actually reflect care that is sensitive to
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9 the particular needs of these patients. Most guidelines do not provide explicit guidance on
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11 treatment of patients with co-morbidity. Guidelines should be more explicit about the
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13 applicability of their recommendations to patients with co-morbidity (58). However, this is
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15 not helped by the lack of clinical trials that include patients with multi-morbidity (59).
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20 A recent systematic review shed some light on what type of primary care based
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22 interventions might be effective to improve health outcomes of patients with multi-
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24 morbidity (60). That review identified ten studies and their results suggested that
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26 organizational interventions which either targeted specific risk factor management, or
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28 focused on areas where patients have more difficulties (such as medicines management),
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30 were more likely to be effective. However, other organizational interventions with a broader
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32 focus (notably case management or changes in care delivery), or patient oriented
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34 interventions that are not linked to healthcare delivery, appeared to be less effective. These
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36 findings provide some evidence for what can be considered to constitute high quality of
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38 healthcare for patients with multi-morbidity. However, more research is needed to confirm
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40 the results.
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49 *Implications*

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52 *Health policy* Although far from conclusive, the evidence suggests that the quality
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54 of care for specific conditions is enhanced in the presence of concordant conditions and
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56 possibly also impaired in the presence of discordant conditions. Efforts are needed to
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3 ensure that continuity and coordination of care for these patients is ensured (61), as the
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5 evidence suggests that patients with multi-morbidity recognize the potential for
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7 improvement in these areas. Interestingly, the evidence suggests that complex models of
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9 care (such as case management) do not necessarily pay off and when it does, it may not be
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11 scalable to the wider majority of patients with multi-morbidity (60), making the use of
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13 already available alternatives, such as the enhancement of primary care services, a valid and
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15 potentially more efficient response (62). Importantly, until we have a better understanding
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17 of the implications of multi-morbidity for quality, not to mention the availability of multi-
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19 morbidity specific indicators, incentives systems that reward quality of healthcare should be
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21 more cautious in their definitions of eligible populations, allowing for the exclusion of
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23 selected patients from the incentives system based on clinical criteria (this is already the
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25 case for the Quality and Outcomes Framework, the Primary Care pay for performance
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27 system in the United Kingdom) (63).
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34 *Research* There is no doubt that we need more and better designed epidemiological
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36 research on the impact of multi-morbidity on quality and safety (3). In that sense, so far the
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38 vast majority of the studies on this area have been conducted in the US, and there is very
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40 limited information from European countries - where well-developed primary care systems
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42 are more frequent. We cannot simply expect that the results from the studies in the U.S are
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44 transferable to European countries. In order to increase our understanding of the
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46 magnitude and nature of the impact of multi-morbidity on quality of healthcare in the
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48 European context health system-specific research is very much needed. We also need
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50 research that helps us understand how to make best use of the available tools; e.g., how
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52 best to systematically integrate evidence from different clinical practice guidelines for
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3 providing care for these complex patients (64). There is also a substantial lack of evidence
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5 on what is the impact of multi-morbidity at the population level (the mix of conditions in the
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7 population served by a primary health care provider) on the organisation and delivery of
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9 healthcare. Moreover, a greater emphasis in the incorporation of patient-reported
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11 information in multi-morbidity studies is needed in order to account for patients' perception
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13 of those problems that interfere more in their everyday lives.
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20 *Clinical practice* What now for busy clinicians for whom multi-morbidity is the bread
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22 and butter of their daily practice? Clinicians should approach the management of patients
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24 with multi-morbidity much as they would approach the management of any given group of
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26 patients: carefully weighting up the evidence supporting any recommendations for that
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28 particular group and tailoring to each individual's needs. Given the current state of the
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30 evidence, if there ever was a dichotomy between art and science in medicine, this is clearly
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32 an area where clinical practice is closer to the former than to the latter. The principles of
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34 Minimally Invasive Medicine (65) and patient-centred medicine (66) might provide helpful
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36 guidance for decision-making in everyday practice for patients with multi-morbidity.
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45 *Conclusions*

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48 Although patients with multi-morbidity are in theory at higher risk of receiving poor quality
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50 of healthcare, the evidence is inconsistent and suggests that there may also be potential
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52 benefits of current arrangements for the delivery of care. Indicators of the quality of
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54 healthcare that are based on available evidence are very much needed before progress can
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56 be made in this field. In the absence of evidence for the benefits and harms of available
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3 management options clinicians should be thoughtful when delivering care for these
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5 patients, using minimally invasive medicine and patient-centred medicine as guidance for
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7 everyday practice. Health systems should focus on enhancing primary care centred
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9 coordination and continuity of care and designing incentives systems that reward
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11 appropriate care for these patients.
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19 **Conflict of Interest:** The authors declare no conflict of interest
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Box 1. Methodology used for the literature review

- To identify relevant studies, one reviewer searched Medline for studies of any design published from inception to February 2015 (search strategy available in the online supplemental table 1).
- The bibliographic search also included a manual search (using free keywords) in Google Scholar and the examination of the references included in relevant studies that were identified a priori.
- To be eligible for inclusion, studies had to include empirical research examining the quality of healthcare provided to patients with multi-morbidity in the context of primary care.
- Four separate multi-morbidity constructs were taken into account:
 - Multi-morbidity: the presence of more than one distinct condition in an individual.
 - Co-morbidity: any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study.
 - Morbidity burden: overall impact of the different diseases in an individual taking into account their severity.
 - Clinical complexity: the overall impact of the different diseases in an individual taking into account their severity and other health-related attributes.
- Quality of healthcare was conceptualized according to the definition proposed by Campbell et al. (15): “whether individuals can access the health structures and processes of care which they need and whether the care received is effective”.
- All studies falling into these conceptualizations were included, regardless of the methodology used to measure quality and multi-morbidity.
- We did not exclude studies based on language, country- or date of publication.
- Initially, references’ titles and abstracts were screened for relevance. Subsequently, identified articles’ full-text was read.
- Findings were extracted using a structured template.

Box 2. Main findings from the literature review

- The bibliographic search retrieved 1,622 unique references. After abstract and full text screening, 37 relevant empirical studies examining the association between multi-morbidity and quality of healthcare were identified (16-52).
- All the studies published during the last decade, mostly in the United States.
- The studies included measures of multi-morbidity (absolute number of health conditions), co-morbidity (health conditions present in addition to an index disease) or morbidity burden (using metrics that take into account both the number and severity of conditions), but none of them measured patient complexity (which additionally considers socio-demographic characteristics of the individuals).
- Quality of healthcare was measured based on condition specific indicators of processes of care and/or intermediate outcomes, or on patient reported information of patient centred care.
- Studies on multi-morbidity and morbidity burden suggested that increased severity and number of conditions may be associated with better quality of healthcare as measured by condition specific indicators of processes and intermediate outcomes, but with worse quality of healthcare when it is measured using a patient centred approach, such as patient reported impact.
- Studies analysing the impact of co-morbidity suggested that quality of healthcare measured by condition specific indicators may be enhanced in the presence of synergistic combinations of conditions (i.e., conditions that share a patho-physiological pathway), and possibly impaired by the presence of antagonistic or neutral conditions.

Table 1. Evidence for the impact of multi-morbidity on quality and safety of healthcare.

Study	Measurement of Multi-morbidity	Measurement of Quality of Healthcare	Observed association*
Mand, 2014 (43)	Number of conditions (Beers list)	Number of potential drug-disease interactions	Direct association
Min, 2014 (44)	Number of general medical (atrial fibrillation, coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, hypertension) and geriatric (hearing impairment, dementia, falls, urinary incontinence, malnutrition, and osteoporosis) conditions	65 ambulatory-care quality indicators related to care processes	Direct association for general medical multi-morbidity (indirect association for geriatric multi-morbidity)
Tsang, 2013 (45)	Number of conditions (Expanded Diagnostic Clusters in ACG system).	Incidence of recorded iatrogenic harm in general practice	Direct association
Schnitzer, 2012 (33)	Patients with at least three diseases or explicitly self-reporting to have multi-morbidity	Patient complaints	Inverse association
Woodard, 2012 (41)	Number of the following conditions (in addition to diabetes): hypertension, ischemic heart disease, hyperlipidemia, depression, arthritis, and chronic obstructive pulmonary disease. Patients were classified as having 0, 1, 2, or 3 of these	Quality of diabetes care (intermediate outcomes)	Direct association

	comorbidities		
Gulliford, 2011 (24)	Number of patient reported long-term conditions. Patients were classified as having 0, 1, 2, 3, or 4 long-term conditions.	Patient-reported experiences of healthcare (relational and management continuity)	Inverse association for management continuity. No association for relational continuity.
Fung, 2008 (23)	Two approaches were used: 1. Count of individual conditions: the number of chronic conditions co-occurring in each participant was summed, without considering any concordance among the conditions 2. Count of condition groups: concordant conditions were grouped together and the number of condition groups co-occurring in each participant was counted. Patients were subsequently allocated to the following groups: 0 condition groups, 1-2 conditions groups, and 3 or more condition groups.	Composite measure of patients' ratings of patient-physician communication.	Inverse association
Higashi, 2007 (27)	Total number of chronic conditions affecting each patient	Quality indicators related to care processes covering 30 clinical conditions and preventive care	Direct association
Min, 2007 (29)	Coexisting combinations of 8 conditions (hypertension, coronary artery disease, chronic obstructive pulmonary disease,	Quality indicators related to care processes covering 15	Direct association

	osteoarthritis, diabetes mellitus, depression, osteoporosis, and atrial fibrillation)	clinical conditions and preventive care	
Parchman, 2005 (30)	Patients with single chronic illness compared to those with multiple chronic illnesses.	Patient-reported experiences of healthcare	Inverse association

* A direct association is one in which an increase in the number of conditions is associated with an increase in quality and safety of healthcare; and indirect association is one in which an increase in the number of conditions is associated with a decrease in quality and safety of healthcare.

Table 2. Evidence for the impact of morbidity burden on quality and safety of healthcare.

Study	Measurement of morbidity burden	Measurement of Quality of Healthcare	Observed association*
Woodard, 2012 (41)	Morbidity burden was measured with the “Diagnostic Cost Group Relative Risk Scores” (consisting in a ratio of the patient’s predicted cost to the average actual cost of the patient population)	Quality of diabetes care (intermediate outcomes)	Direct association
Burgers, 2010 (18)	‘Morbidity score’, consisting in a combination between the number of conditions and patient-reported health status	Patient-reported experiences of healthcare	Inverse association
Werner, 2008 (40)	Diagnostic cost groups–hierarchical condition categories (DCG) model, which uses age, sex, and diagnoses to summarize a patient’s medical conditions	Quality indicators covering clinical conditions and preventive care, and patient reported satisfaction with care	Direct association (all quality indicators and satisfaction with care)
Halanych, 2007 (25)	Charlson Comorbidity Index, which includes 17 specific illnesses and weights them according to severity	Quality indicators covering use of common services for diabetic patients (A1C testing, lipid testing, dilated eye exam, and urinary microalbumin testing)	No association

* A direct association is one in which an increase in the morbidity burden is associated with an increase in quality and safety of healthcare; and indirect association is one in which an increase in the morbidity burden is associated with a decrease in quality and safety of healthcare.

Table 3. Evidence for the impact of co-morbidity on quality and safety of healthcare.

Study	Index condition	Measurement of co-morbidity	Measurement of Quality of Healthcare	Observed association*
Buja, 2014 (46)	Diabetes mellitus	Charlson Comorbidity Index	Quality of diabetes care (guideline consistent processes)	Mixed associations for the different quality indicators. Impact by type of comorbidity was not examined.
Druss, 2012 (21)	Diabetes Mellitus	Having or not one or more mental conditions in addition to Diabetes Mellitus	Quality of diabetes care (intermediate outcomes and hospital admissions)	Indirect association(antagonist)
Pentakota, 2012 (31)	Diabetes Mellitus	Patients were classified into five chronic comorbid illness groups: none, concordant only, discordant only, both concordant and discordant, and dominant.	Quality of diabetes care (guideline consistent processes and intermediate outcomes)	Direct association (synergistic conditions); inverse association (neutral/antagonistic conditions)
Voorham, 2012 (39)	Diabetes Mellitus	Comorbidity was measured taking into account two dimensions: 1) concordance to diabetes (related versus unrelated conditions), and 2)	Quality of diabetes care (Intensification of pharmacological therapy)	Direct association (synergistic conditions); no association otherwise

		degree of priority (considering as high priority those conditions that are life-interfering, incident or requiring new medication treatment)		
Woodard, 2011 (42)	Diabetes Mellitus	Patients were assigned to 1 of 4 condition groups: diabetes-concordant (hypertension, ischemic heart disease, hyperlipidaemia), and/or -discordant (arthritis, depression, chronic obstructive pulmonary disease) conditions, or neither.	Quality of diabetes care (intermediate outcomes)	Direct association (synergistic and antagonist conditions)
Vitry, 2010 (38)	Diabetes Mellitus	Comorbid conditions unrelated to diabetes were identified by using prescription-dispensed data. Potential impact of related to diabetes comorbid conditions was not examined.	Quality of diabetes care (time to therapeutic progression of pharmacological therapy)	Inverse association (neutral and antagonistic conditions)
Ahern, 2007 (16)	Diabetes Mellitus	Charlson Comorbidity Index	Quality of diabetes care (avoidable hospitalizations due to short-term complications and	Direct association (synergistic conditions); Inverse association (antagonistic

			uncontrolled diabetes)	conditions)
Chaudhry, 2005 (19)	Diabetes Mellitus	Charlson Comorbidity Index	Quality of diabetes care (Intensification of pharmacological therapy)	No association Impact by type of comorbidity was not examined.
Desai, 2002 (20)	Diabetes Mellitus	Only mental comorbidities were examined. Patients were categorized into one of four mutually exclusive diagnostic groups: no mental comorbidity; psychiatric comorbidity only; substance (alcohol or drug) use comorbidity only; or dual diagnosis (psychiatric and substance use disorders).	Quality of diabetes care (processes of care and intermediate outcomes)	Indirect association (antagonists)
Doubova, 2013 (47)	Hypertension	Comorbidity was calculated based on the presence of diabetes mellitus and/or chronic kidney disease	Quality of healthcare for hypertension (intermediate outcomes)	Indirect association

Petersen, 2009 (32)	Hypertension	Patients were classified into 4 condition groups: those with hypertension concordant (diabetes mellitus, ischemic heart disease, dyslipidaemia) and/or discordant (arthritis, depression, chronic obstructive pulmonary disease) conditions or neither.	Quality of healthcare for hypertension (guideline consistent processes and intermediate outcomes, and satisfaction with care)	Direct association (all synergistic, neutral, and antagonistic conditions)
Turner, 2008 (36)	Hypertension	Patients were classified according to the number of unrelated (antagonist) comorbid conditions (0, 1, 2, 3, 4, 5, 6, and 7 or more unrelated conditions), and related (synergistic) comorbid conditions (single vascular disease, multiple vascular diseases, chronic renal insufficiency, and diabetes).	Quality of healthcare for hypertension (Intensification of pharmacological therapy)	Indirect association (antagonistic conditions)
Ani, 2009 (17)	Depression	Comorbidities were calculated based on the Charlson Comorbidity Index. Patients were classified in three groups: 1) no comorbidity and	Quality of healthcare for depression (diagnosis, guideline-concordant treatment, and follow-up care)	No association. Impact by type of comorbidity was not examined.

		depression alone; 2) with a comorbidity index of 1 to 2 and depression; and 3) with a co-morbidity index of 3 or greater and depression		
Teh, 2008 (35)	Depression	Comorbidity calculated based on the presence of one or more comorbid condition(s) (yes/no), and patient-reported health status.	Patient-reported depression care quality	Direct association for diagnosis of depression and antidepressant prescription. No association with receiving minimally adequate depression care or patient satisfaction. Impact by type of comorbidity was not explored.
Harman, 2005 (26)	Depression	Comorbid diabetes mellitus, hypertension, heart disease, and arthritis in older persons with depression were identified from patient self-report.	Depression treatment	Direct association with hypertension and diabetes. No association for heart disease and arthritis.
Wirtz, 2014 (48)	Cancer (breast)	Charlson Comorbidity Index	Annual receipt of surveillance mammography	Indirect association Impact by type of comorbidity

				was not explored.
Fisher, 2007 (22)	Cancer (colorectal)	Comorbidity measured with an adaptation of the Charlson Comorbidity Index	Colorectal Cancer Screening	No association. Impact by type of comorbidity was not explored.
Virani, 2011 (37)	Cardiovascular disease	Comorbidity measured as patients with history of diabetes mellitus (yes/no) and hypertension (yes/no).	Quality of healthcare for hyperlipidaemia (Intensification of pharmacological therapy)	Direct association (synergistic conditions)
Lagu, 2008 (28)	Cardiovascular risk factors (including hypertension and hyperlipidemia)	Concordant comorbidity was calculated as the sum of the following conditions: diabetes, coronary artery disease, coronary artery disease equivalent and renal insufficiency. Discordant comorbidity burden was calculated from an adapted version of Elixhauser's comorbidity measure (which uses ICD-9-CM-codes to identify 29 specified conditions associated with inpatient resource use and mortality).	Quality of healthcare for hyperlipidaemia (guideline consistent processes and intermediate outcomes)	Direct association (synergistic conditions); Inverse association (antagonistic/neutral conditions)

Cancian, 2013 (49)	Chronic heart failure	Presence of another cardiovascular condition (ischaemic heart disease, atrial fibrillation), or other conditions (chronic obstructive pulmonary disease, renal failure, dementia)	Pharmacotherapy (adherence to evidence-based recommendations) and chronic heart failure related hospitalizations	Pharmacotherapy: Direct association for ischaemic heart disease, and indirect for chronic obstructive pulmonary disease and dementia. Hospitalizations: direct association for coronary disease aetiology, atrial fibrillation, kidney failure and chronic obstructive pulmonary disease
Frigola-Capell, 2013 (50)	Chronic heart failure	Number of comorbidities, including; hypercholesterolemia, hypertension, diabetes mellitus, ischaemic heart disease, chronic obstructive pulmonary disease and chronic kidney disease	Pharmacotherapy (prescription of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers).	Direct association between the number of comorbidities and the prescription of recommended treatments. Impact by type of comorbidity was not explored.

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Werner-Busse, 2014 (51)	Atopic dermatitis	One or more atopic conditions (allergic asthma, urticaria, allergic rhinitis and food allergy)	Adherence to evidence-based treatment recommendations	Direct association. Impact by type of comorbidity was not explored.
Sharif, 2013 (52)	Chronic obstructive pulmonary disease	Number of conditions, including: hypertension or other cardiovascular disease (coronary artery disease, chronic heart failure, ischemic or non-ischemic cardiomyopathy), diabetes mellitus, anxiety or depression, osteoporosis, and lung cancer	Providers' adherence to the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the pharmacotherapeutic management of patients with stable chronic obstructive pulmonary disease	No association. Impact by type of comorbidity was not explored.
Singh, 2009 (34)	Gout	Charlson Comorbidity Index	Adherence to evidence-based recommendations	Indirect association Impact by type of comorbidity was not explored.

* Synergistic conditions are those that represent parts of the same overall pathophysiologic risk profile and are more likely to be the focus of the same disease and self-management plan. Antagonistic conditions are those not directly related in either their pathogenesis or management. A direct association is one in which an increase in number of comorbid conditions is associated with an increase in quality and safety of healthcare; and indirect association is one in which an increase in the number of comorbid conditions is associated with a decrease in quality and safety of healthcare.

Online appendix table 1. Search Strategy

	Search terms
1	exp Safety Management/ or exp Patient Safety/ or patient safety.tw. or safety culture.tw. or (safe\$2 adj2 (practice? or management?)).tw. or (st.fs. and (safe or safety).tw.)
2	Quality Assurance, Health Care.mp. or exp Quality Assurance, Health Care/ or exp *health care quality/
3	1 or 2
4	exp Comorbidity/
5	(comorbid\$ or co-morbid\$).ti,ab.
6	(multimorbid\$ or multi-morbid\$).ti,ab.
7	(multidisease? or multi-disease? or (multiple adj (ill\$ or disease? or condition? or syndrom\$ or disorder?))).ti,ab.
8	4 or 5 or 6 or 7
9	exp General Practice/ or exp Ambulatory Care/ or exp primary health care/ or (((primary or community) adj2 (care? or health\$ or service?)) or (ambulatory adj2 (care or service))).tw.
10	3 and 8 and 9