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Causes and consequences of comorbidity: A review

RONALD GIJSEN [A,*], NANCY HOEYMANS [A], FRANÇOIS G. SCHELLEVIS [B], DIRK RUWAARD [A], WILLIAM A. SATARIANO [C], GEERTRUDIS A.M. VAN DEN BOS [A,D]

[a]National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands
[b]Netherlands Institute of Primary Health Care (NIVEL), Utrecht, The Netherlands
[c]School of Public Health, University of California at Berkeley, Berkeley CA, USA d Department of Social Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
*Corresponding author. Tel.: +31 30 2743950; fax: +31 30 2744450. E-mail address : ronald.gijsen@rivm.nl (R. Gijsen)

ABSTRACT

A literature search was carried out to identify and summarize the existing information on causes and consequences of comorbidity of chronic somatic diseases. A selection of 82 articles met our inclusion criteria. Very little work has been done on the causes of comorbidity. On the other hand, much work has been done on consequences of comorbidity, although comorbidity is seldom the main subject of study. We found comorbidity in general to be associated with mortality, quality of life, and health care. The consequences of specific disease combinations, however, depended on many factors. We recommend more etiological studies on shared risk factors, especially for those comorbidities that occur at a higher rate than expected. New insights in this field can lead to better prevention strategies. Health care workers need to take comorbid diseases into account in monitoring and treating patients. Future studies on consequences of comorbidity should investigate specific disease combinations.

1. INTRODUCTION

The aging of populations is a worldwide phenomenon, especially in Western societies. In 1990 the proportion of those 65 years or over ranged from 11% to 18% in Japan, Western Europe, North America, and Australia. This percentage is expected to increase to approximately 19–26% in 2025 [1]. Because many health problems are known to increase with age, this demographic trend may lead to an increase in the absolute number of chronic conditions in the population. In addition, because there is a growing body of evidence that older people are at risk for multiple, comorbid conditions, the prevalence of comorbidity in the general population, as well as among those seeking health care, will probably also increase and become a common phenomenon.

Comorbidity refers to one or more other diseases among people with an index-disease (e.g., cardiovascular disease) [2,3]. In elderly populations, comorbidity occurs frequently, as can be illustrated by three examples. In a Dutch General Practice population, 79% of the elderly with a chronic health condition had one or more comorbid diseases [4]. A Dutch cancer registry found that the prevalence of comorbidity among incident cancer patients ranged from 12% among patients younger than 45 years to 60% among patients of 75 years or older [5]. Finally, the Duke Established Populations for Epidemiologic Studies of the Elderly showed that older persons with hypertension, coronary artery disease, cerebrovascular disease, diabetes, and cancer reported substantial comorbidity

[6]. This ranged from 47% among those with hypertension to 88% among those with cerebrovascular disease.

An international expert meeting on comorbidity and chronic diseases, organized by the Netherlands Organization for Scientific Research (NWO) in 1996, concluded that the importance of comorbidity is clear, due to its high prevalence in older populations and its impact on health and health care. However, despite the growing number of studies, it also was concluded that comorbidity has been rarely studied as an autonomous phenomenon [7], and more research is needed into the etiology and consequences. The present review was conducted to accumulate and summarize the available information in the recent literature on causes and consequences of comorbidity of a wide range of chronic somatic diseases in order to give more specific recommendations for future research, public health and health care practice. Outcomes to be studied were mortality, functional status or quality of life, and health care (health care utilization, treatment strategy, complications of treatment and discharge destination or readmission to hospital).

2. METHODS

To organize our review findings about the causes and consequences of comorbidity, we used an extension of the general, integrative public health model, commonly applied to study the epidemiology of diseases (Fig. 1). The selection of the index-diseases was based on the burden of disease for patients and society in terms of mortality and/or morbidity (prevalence and severity), excluding mental diseases [8,9]. In case of a broad disease category, a selection of the most important diseases (in terms of burden of disease) was made; for cancers: breast cancer, lung cancer, colorectal cancer, and prostate cancer; for central nervous system diseases: Parkinson's disease, multiple sclerosis, epilepsy, and migraine; for cardiovascular disease: myocardial infarction, angina pectoris, stroke, heart failure, aneurysms of the abdominal aorta, and intermittent claudication; for obstructive lung diseases: chronic obstructive pulmonary disease (COPD) and asthma; and for musculoskeletal diseases: osteoarthritis and rheumatoid arthritis. These somatic diseases were considered in combination with any comorbid disease, including mental disorders and infectious diseases.

[FIGURE 1]

It is sometimes difficult to determine whether a disease should be thought of as a "comorbid disease" (i.e., a separate disease) or as a "complication" of another disease. A workable definition of a complication is the existence of a second disease when the occurrence of an index-disease is required (e.g., diabetic retinopathy and diabetes mellitus) [10]. For the purposes of this review, we included articles about "complications" only in case the authors did label the combination of a disease and complication as comorbidity. For example, ischaemic heart disease was identified as a comorbid disease and not as a complication in a study of the medical costs associated with diabetes [11]. In addition, complications of a treatment (e.g., infection, death or ischaemia following an operation) were regarded as outcome variables and not as comorbidity.

A search was performed of the Medline databases from January 1993 through December 1997. The keyword 'comorbidity' or a related term (such as co–morbidity, multiple pathology, disease clustering, multimorbidity) was included as search criterion. Additional criteria for inclusion were: English language, human subject, no case-reports or tutorials, journal articles (no letters to the editor or comments), and the availability of an abstract in Medline. For this literature review, we performed three search strategies, executed beside one another. For the second and third search strategy (see below) we made use of Medical subject headings (Mesh headings) for the selected index-diseases, combined with the terms "complications," "epidemiology," "mortality," "psychology," "etiology," "genetics," "physiopathology," "pathology," and "prevention-and-control" as subheadings (or no subheading). The detailed search profile can be obtained on request, but in short, the three search strategies are as follows:

1. Comorbidity-related terms in the title. We excluded articles that dealt only with mental disorders or substance- related disorders. This strategy provided articles in which comorbidity was the main subject, whether or not with the selected index-diseases under study.

2. Comorbidity-related terms in the abstract and one of the index-diseases in the Mesh headings (including the subheadings), in order to select articles in which comorbidity was an important variable, and with at least one of the selected diseases.
3. Comorbidity-related terms in the abstract, terms for population-based studies (health survey, geriatric assessment, interviews, questionnaires, population-surveillance, mass-screening) as Mesh heading, and one of the selected diseases as Mesh heading (including the subheadings). Because population-based studies often use comprehensive disease categories, we used the broad disease categories (see Fig. 1) as definition for the diseases. This strategy provided articles in which comorbidity was an important variable, and in which the study design was population based, using broad disease categories (e.g. 'do you have a lung disease?).'

A total of 505 articles, published between 1993 and 1997, were identified. The abstracts of those articles were screened by the first two authors (R.G., N.H.). All articles that met the following criteria were included in the final review:

- one of the selected disease groups was an index-disease;
- study outcome included mortality, functional status, quality of life, or health care.

Exclusion criteria were:

- comorbidity was a part of a classification system of diseases or disease stages;
- comorbidity was a confounder without referral in the abstract to the effects of comorbidity on the outcome.

Both authors screened the first 75 articles. After the first 25 articles, discrepancies ($n = 3$) were discussed and the criteria were sharpened. This procedure was repeated for another 50 articles. The discrepancy was 4 articles. The remaining records were distributed between the two authors. Finally, 82 articles met our inclusion criteria, of which 4 concerned causes of comorbidity and 78 concerned consequences. The most important reasons for excluding articles in the selection were: the disease was not one of the selected diseases, comorbidity was included only as a confounder, or comorbidity was just once mentioned in the introduction or discussion of the abstract.

3. RESULTS

3.1. Methodological aspects

The most important methodological characteristics of the selected articles are presented in Tables 1 and 2. More extensive tables can be found on the internet pages of the journal and of the National Institute of Public Health and the Environment (RIVM) (internet address of the *Journal of Clinical Epidemiology*: www.sciencedirect.com/web editions; internet address of the RIVM: www.rivm.nl/public health/phsf/download/comorb2001pdf). Comorbid diseases were assessed by different methods, including medical records in electronic databases, medical charts, physical examination, personal interviews, and self-reports using written questionnaires. In investigating the effects of comorbidity, comorbidity was expressed in three different ways: by the co-occurrence of specific diseases in individuals with an index-disease (for example COPD in stroke patients), by a simple summing up the number of diseases present in one individual (a comorbidity count), or by a comorbidity index that combines the number and severity of the diseases. An example of such an index has been developed by Charlson [94]. The so-called Charlson Comorbidity Index is a weighted index of comorbidity in which the weights are based on the observed association with 1-year mortality risk in a cohort of hospitalized patients. The index assigns a weight of 1 to 6, according to the risk of mortality, to each of the 19 defined comorbid conditions. The Charlson index is the sum of the weights for each comorbid condition, and can range from 0 to 33. This index is mainly useful in studies with mortality as outcome variable and in which the occurrence of diseases is assessed by interview, anamnesis, medical examination or screening of the medical charts. The Charlson index was used in 11 studies [17,18,22–24,34,38,39,50,63,84].

[TABLES 1-2]

Some studies used a modified version of the Charlson index in which the index-disease was excluded [78,81,85] or adaptations developed by Deyo et al. [95] and Romano et al. [96] for use with administrative databases [42,79,93]. Another type of adaptation of the Charlson index was found in a study on the association between comorbidity and in-hospital mortality in patients who underwent coronary artery bypass surgery [35]. The original weights of the Charlson index were substituted by study-specific weights. The researchers used their own data to derive weights based on the association of the conditions (selection of conditions based on Charlson index) with in-hospital mortality. Not surprisingly, the researchers found that their index was a stronger predictor of mortality than the original Charlson index.

The Index of Coexistent Disease (ICED) [97] is an index that specifically controls for comorbidity when the outcome is functional status. It is based on two dimensions: the severity level of 14 diseases and the severity level of 11 dimensions of physical and mental impairment. For each disease, a patient is placed on a 4-point scale, and for each impairment a patient is placed on a 3-point scale. Finally, the peak scores of these two dimensions are summarized into a 4-point scale, from 0 to 3. We found three studies that used this index [23,60,87].

Seven other weighted indexes were found [16,18,23, 53,63,65,77,83]. For example, a simple weighted index was used by Satariano and Ragland [16]: diseases not independently associated with mortality were weighted zero, whereas those diseases independently associated with mortality were weighted 1. A final score was obtained from the sum of these weights. Liu et al. also developed a weighted index from an examination of 130 conditions. Six severity grades were used. These grades were based on the need for treatment and limitations in daily activities or exercise [63].

3.2. Index-diseases

In the 82 studies of comorbidity, cardiovascular diseases were most frequently studied as index-diseases (48%). The second most studied index-diseases were cancers (23%), followed by musculoskeletal diseases (13%) and diabetes mellitus (11%). Obstructive lung diseases and central nervous diseases were studied the least often (respectively 7% and 5%). These percentages add up to more than 100%, because some studies included more than one index-disease.

3.3. Causes

Only 4 articles examined in the causes of comorbidity (Table 1). These articles identified genetic susceptibility and family history as possible causes. Genetic and familial studies were based on the examination of conditions that occurred more frequently than would be expected by chance alone. For example, migraine and epilepsy co-occurred, often as a result of head trauma [12]. However, patients with these diseases did not share a genetic susceptibility for both diseases [13]. Moreover, neither migraine and arthritis nor hypertension and ischaemic heart disease shared a genetic variation [14].

3.4. Consequences: study characteristics

Seventy-eight articles addressed the consequences of comorbidity. Of these articles, 35 examined the risk of death; 24 examined functional status or quality of life; and 27 focused on a variety of health-care outcomes. These numbers add up to more than 78, because some papers reported the effects of comorbidity on more than one outcome (Table 3). As noted previously, cardiovascular diseases and cancers were most likely to be included as index-diseases.

[TABLE 3]

Of the 78 outcome studies, 6 studies were population based, 16 studies were based on registrations that covered all or most of the patients with the selected disease(s) in a certain region, 17 studies were based on registrations that covered a particular selection of the patients with the selected disease(s), 1 study on a General Practice population, 37 studies were based on patients in one or a few hospitals and 1 study on patients admitted to a rehabilitation center (Table 4). The comorbid diseases covered a broad spectrum of diseases, and in studies dealing with functional status or quality of life, often mental disorders were included as comorbid diseases. Infectious diseases were only included in one study [67], although infectious diseases or their sequelae were sometimes incorporated in indexes or counts.

[TABLE 4]

3.5. Consequences: mortality

The 35 studies including mortality as outcome are summarized in Table 2. Most of these were hospital based. Mortality was defined in different ways: from in-hospital mortality (12 studies) to 30-day mortality (3 studies) to 22-year mortality. Only three studies distinguished cause-specific mortality (mortality from the index-disease, i.e., breast cancer or prostate cancer, versus mortality from other causes) [16,23,24]. Index-diseases were mainly lethal diseases. Predominantly studied were cardiovascular diseases and to a lesser degree cancers. Other index-diseases were diabetes mellitus with renal failure and severe COPD. In 24 cases the effects of the comorbid diseases were studied as specific combinations with the index-disease (pairs), but in 14 studies a comorbidity count or comorbidity index was used.

As Table 2 shows, comorbidity, either recorded as an index or as a simple count, was significantly related to mortality in almost all studies [16–18,23,24,32,34,35,38,39, 42,46]. Only two studies showed no significant effect [22,50]. In one study of older patients with severe COPD, other strong prognostic variables were found. Comorbidity did not have a significant effect after adjustment for chronic renal failure, right ventricular hypertrophy or overload, forced expiratory volume in 1 s, ischaemic heart disease and age [50]. A comorbidity index or count can be a strong determinant of mortality, sometimes even after adjustment for clinical signs or other diseases (e.g. [32,46]. However, if the clinical signs or other diseases have a strong effect on mortality, the extra effect of comorbidity, expressed by an index, can be low.

The effects of specific combinations of diseases on mortality were not always consistent. For example, in one study patients with a nonruptured aneurysm of the abdominal aorta had a higher risk for death within 30 days when they also had ischaemic heart disease, heart failure or renal disease [47]. In another study, patients with these combinations of diseases did not have a higher risk [48]. In total, 9 studies found that all disease combinations studied were significantly related to mortality [21,25,28,30,32,33,39, 47,49], four studies found no combinations of diseases with a higher risk on mortality [40,44,45,51], and the remaining 11 studies found some combinations with a higher risk on mortality, and some without an elevated risk. Some general patterns could be observed. In studies with a relatively longer follow-up period (1 month or longer), most comorbid diseases were significant predictors of mortality, especially when these diseases affected vital organs (cardiopulmonary system, kidneys), such as ischaemic heart disease, congestive heart failure, COPD and renal failure. Findings also indicated that comorbidity was not independently associated with mortality in situations in which (a) the index-disease was especially lethal and (b) when the explanatory model included a number of clinical variables associated with the index-diseases (e.g., [40,44,45]).

3.6. Consequences: functional status or quality of life

Twenty-four articles examined functional status or quality of life (Table 2). There were 6 prospective observational studies [52,54,59,61,65,75] and 18 cross-sectional studies. Index-diseases included a variety of conditions, in particular, a relatively large number of cardiovascular and musculoskeletal diseases.

Twelve studies included a comorbidity index or count, and in 10 studies this was significantly related to the outcome [55,56,60,63,65,67,68,72–74]. In one study, concerning the relation between chronic comorbid diseases and physical function, only in younger patients (< 60 years) was a significant association observed [54]. In a study of cancer patients, comorbidity was significantly related to quality of life only for prostate cancer, but not for lung cancer and colon cancer. The researchers adjusted for many confounders, including performance status [53].

Specific disease combinations also were studied. Of the 14 studies, two reported that all disease combinations were significantly related to functional status or quality of life [57–71]. Three other studies found no single combination of diseases associated with a higher risk for impaired functional status or quality of life [52,61,65]. The remaining nine studies found that the risk for an impaired functional status or quality of life depended on the combinations of diseases and/or on the specific dimension of quality of life [58,59,62,64,66,69,70,74,74].

Some consistent patterns could be observed. All comorbid conditions increased the risk of impaired functional status or quality of life among patients with diabetes mellitus, Parkinson’s disease, and

respiratory diseases [55–59,67,68]. For cancer, cardiovascular diseases and musculoskeletal disorders, the effect of comorbid conditions was variable. For some comorbid diseases, an effect was seen in some dimensions of quality of life, but not others. Mental disorders as comorbid diseases were shown to increase the risk for an impaired functional status or quality of life in all studies [57–59,70,71], but one [53].

3.7. Consequences: health care

Twenty-seven articles addressed the consequences of comorbidity for different aspects of health care (Table 2): health care utilization, including hospital costs and length of stay (8 studies), treatment strategy (9 studies), complications of treatment (5 studies), and studies with discharge disposition or readmissions as outcomes (5 studies). Almost half of the studies (n = 12) were based on patients in a single hospital or rehabilitation center, and the other half (n = 14) was based on registries of more than one hospital. Only one study was population based. Index-diseases were mainly cardiovascular diseases and cancers, and to a lesser degree diabetes mellitus and rheumatic diseases.

All eight studies concerning comorbidity in relation to health care utilization (mainly hospital care) found a significant relationship. In six of these studies, comorbidity was expressed as a count, index or simple dichotomy. Two studies looked at specific combinations of diseases: the study of comorbid depression in relation to rheumatoid arthritis found that depressed patients reported more physician visits and hospitalization than nondepressed patients [71]; and the study on comorbid cardiovascular diseases in diabetic patients found heart disease and hypertension to significantly increase the medical costs [11].

Nine studies had treatment strategy as the outcome. Six of these studies concerned cancer and in five of these, a significant effect of comorbidity was observed. Increasing levels or severity of comorbidity reduced the chance of receiving any therapy or surgical therapy for lung cancer [81] and primary resection for colon cancer at the expense of staged resection and palliative intervention [19]. However, according to the authors in the latter case, a less radical therapy was justified for patients with comorbidity because it led to a better survival. In one study of patients with breast cancer, increasing age, but not comorbidity, was associated with a reduction in the likelihood of lymph node dissection and the use of adjuvant therapy after surgery [85]. In other studies of breast cancer, the presence of comorbidity decreased the likelihood of standard therapy [82], surgical therapy [84] and breast-conservative surgery and axillary dissection [83,84]. Although this was not in accordance with the established guidelines, it is possible that this was the best strategy for patients with comorbidity. Patients with comorbidity may be too vulnerable for the additional radiotherapy or chemotherapy, necessary after breast-conservative surgery and axillary lymph node dissection. Among patients who survived a myocardial infarction, comorbidity decreased the likelihood of using thrombolytics and aspirin [32,86,87]. In this case, the authors recommended improvements in the care of critically ill patients and suggested further research into patient, family, and physician factors that may explain this finding.

The relation between comorbidity and complications of treatment was more complex. In all five studies, specific disease combinations were studied. Some combinations were significantly related to complications of treatment, while others were not. Diabetes mellitus as a comorbid disease was significantly related to complications of treatment in four of the five studies. It was suggested that the pathophysiological process was due primarily to vasculopathy or atherosclerosis [89,90], which caused stroke, septicaemia (via ischaemia of the arteries of the gastrointestinal tract and consequently a breakdown of the mucosal–blood barrier), neuropathy (which causes skin infections and consequently septic arthritis), a diminished cellular immune response (via hyperglycaemia) [92] and/or an increased chance of hypoglycaemia secondary to heart failure [88]. Another noteworthy finding was that renal insufficiency, cardiovascular diseases, and COPD were significantly associated with complications of treatment in only one of the five studies in which these comorbid conditions were examined. One study found no effect of comorbidity on complications of treatment at all [9].

In three of the five studies on readmissions or destiny of discharge, comorbidity showed some effect. For example, among diabetes patients who received an amputation of (a part of) their leg(s), those with peripheral vascular disease, a locomotor impairment, or a stroke had a greater chance of being discharged to a rehabilitation facility or a nursing home. For other comorbid diseases, no associations were found [27]. The comorbidity index increased the chance of readmission or death for patients with

congestive heart disease [39,93], but no effect of the comorbidity index was observed for stroke patients [42,65].

4. DISCUSSION

In this article, we gave an overview of the comorbidity studies concerning either causes or consequences of comorbidity, published between 1993 and 1997. The concept of comorbidity has been receiving increasing attention, as evidenced by the large and increasing number of studies each year; in our literature search the number of studies increased from 53 in 1993 to 141 in 1997. As such, we recommend that reviews of this kind be conducted from to time to time to monitor the trends of research in this area. In this discussion section, we briefly describe our findings and draw some general conclusions from them. From these results and general conclusions we give recommendations for further research and for health care practice.

4.1. Methodological aspects

We excluded mental disorders as index-diseases because managing somatic as well as mental disorders would be too extensive for one literature review. Including mental disorders would have added another 1653 articles to our search. Comorbidity in psychiatry is an important topic; it requires a systematic examination [98].

Our search strategy identified 505 articles about comorbidity of somatic diseases, of which 82 met our inclusion criteria. Given the diversity of articles on comorbidity, it is difficult to identify a comprehensive search strategy. No doubt, some articles were missed. Missed articles would have included those that focused on two or more conditions, but did not include “comorbidity” (or related terms) in the title, abstract or as Mesh heading. A closer look into a sample of this kind of article pointed out that these studies mainly dealt with the combination of diabetes mellitus and cardiovascular diseases.

Another possible limitation of our search strategy is the introduced publication bias in selecting articles about consequences. We selected only articles that referred to absence or presence of effects of comorbidity on outcome in the abstract. Therefore, we missed articles in which the relation between comorbidity and outcome was studied but no information was given in the abstract.

4.2. Causes of comorbidity: findings and recommendations for research

Our search led to only four articles about causes of comorbidity. We did not search for articles on the occurrence of comorbidity, although these articles are likely to contain information on the distribution by age, sex, and possibly other sociodemographic variables. In spite of this potential limitation, we conclude that there are very few articles on causes of comorbidity. We did not find a single study on biological risk factors (such as cholesterol, blood pressure, obesity), life style (smoking, drinking, nutrition, physical activity), environmental factors (air pollution, social environment), or medical factors. However, this conclusion must be taken with care, because of the above-mentioned considerations about the literature on specific combinations.

We recommend more studies into causes of comorbidities, with emphasis on shared risk factors. Most interesting are studies involving causes of disease clustering. Disease clustering means co-occurrence of diseases at a significantly higher rate than is expected. Knowledge about causes of disease clustering can hopefully lead to better prevention strategies, including early recognition of secondary diseases.

4.3. Consequences of comorbidity: findings

About half of the studies looked at the impact of comorbidity operationalized as a count of comorbid diseases or as a comorbidity index. The other half included studies on specific combinations of diseases. With few exceptions, all studies that used a count or index found a significant effect of comorbidity on mortality, functional status, quality of life, and different aspects of health care, frequently after adjustment for a large variety of covariates, including clinical variables. From this we conclude that, in different settings, with different study designs and outcome measures, and even after adjustment for different confounders, comorbidity in general does affect health outcomes.

Not all combinations of index-diseases and comorbid diseases showed an effect on outcomes, but some consistent associations were found. Diseases that affect systems that are essential for maintaining physiological homeostasis (cardiopulmonary and renal system) were significantly related

to mortality. Comorbid mental disorders were significantly associated with functional status or quality of life. Furthermore, comorbidity was consistently related to health care utilization (costs, length of hospital stay, and number of physician visits). Differences in effect observed between some studies can be explained by the number of patients in the study, the confounders taken into account (such as stage of disease), and other characteristics of the study design (retrospective, prospective or cross-sectional).

4.4. Consequences of comorbidity: recommendations for research

Since comorbidity in general is significantly related to mortality, functional status, quality of life and different aspects of health care, studies on the relationship between diseases and these outcomes should take comorbidity into account. If comorbidity or specific disease combinations is not the subject of interest, comorbidity can be taken into account as a confounder by using a comorbidity index or at least a count of individual conditions. The measurement of comorbidity should preferably be related to the study outcome (e.g., the Charlson Comorbidity Index when the outcome is mortality and the Index of Coexistent Disease when the outcome is functional status).

We found that comorbid mental diseases are significantly associated with functional status or quality of life. The effect of comorbid mental disorders on mortality and health care was seldom studied. Nevertheless, studies in psychiatry show that mental disorders increase the risk for death, not only from suicide but also from other disease categories [99]. In population-based studies higher mortality risks were found for depressive disorders [100–102], schizophrenia [100,101], and alcohol abuse [101,103]. Our recommendation is therefore to study the effect of comorbid mental disorders on mortality, quality of life, as well as on health care. It is further recommended that comorbidity indexes also include mental disorders as well as somatic conditions.

Our analysis did not include studies about multimorbidity, as being the co-occurrence of two or more diseases within one person [104], without defining an index-disease. However, with our search strategy we identified seven studies about multimorbidity within our selection of chronic diseases, one about causes [105] and six about consequences. All studies about consequences of multimorbidity showed a significant effect on outcome: three on mortality [106–108], two on functional status [109,110], and one on length of hospital stay [111]. For gaining more insight into the consequences of the co-occurrence of two or more diseases in one person, research in the field of multimorbidity is recommended. This is especially relevant for describing the health of the general population, as for example in reference [109] and [110] and of frail populations, as for example in geriatry [108] and among critically ill patients [106,107].

In order to further increase our knowledge of the consequences of comorbidity, studies based on specific disease combinations can give the best information. Especially interesting would be investigations to determine whether specific pairs of diseases have a synergistic or dampening effect on specific outcomes. Verbrugge et al. made a start with this type of examination with a study on comorbidity and its impact on disability [112]. They found that some combinations of diseases led to a higher than expected risk on disability. Examples are stroke with hip fracture, diabetes mellitus, or osteoporosis; visual impairment with osteoporosis; and ischaemic heart disease with cancer. Other disease pairs, such as ischaemic heart disease and stroke, had a dampening effect. In our review, we found only two articles in which a synergistic effect was studied [74,75], both on the functional status of patients with osteoarthritis. Combinations of osteoarthritis with visual impairment, hip fracture, atherosclerosis, ischaemic heart disease, pulmonary disease and obesity were found to have a synergistic effect, whereas for osteoarthritis and hypertension a dampening effect was found. Well-designed studies on the synergistic effects of specific combinations have been done by Fried et al. [113] and Newschaffer et al. [114]. In the study of Fried et al. on comorbidity and disability, arthritis and visual impairments, heart disease and cancer, and lung disease and cancer were synergistically associated with disability. In the study of Newschaffer et al., an excess mortality rate for women with breast cancer and comorbidity was reported, but this excess was rather small.

Observations about a synergistic effect associated with specific combinations of conditions on outcomes are important for individual patient care as well as for health care policy, because a large amount of health gain can be achieved by prevention or early recognition and adequate treatment of comorbid diseases. The best strategy to study this phenomenon seems to set up a study that specifically looks at the effects of comorbidity (i.e., follow a group of patients in time and monitor

their functional status, quality of life, health care utilization, and survival in relation to specific comorbidities, taking into account variation by sociodemographic variables). Because the number of persons in such a study would soon reach unworkable quantities, a study might be set up for a limited number of conditions, with special attention for diseases that are seldom included in studies on comorbidity, like central nervous system diseases and obstructive lung diseases.

4.5. Consequences of comorbidity: recommendations for health care

We found that patients with comorbidity had a higher risk of dying, a poorer functional status or quality of life and greater use of health services. These findings led to the conclusion that among patients with comorbidity, the focus of health care should not only be on one specific disease, but also on the pathology in other organs, the worsening functional status, the increasing dependence from care and the increasing risk of mental and social problems. Health care workers can anticipate this by monitoring patients with comorbidity intensively and spending more time per visit with them. They should be alert for a second disease in persons with one disease. This is particularly important in older people. A way to incorporate this into daily practice is to formulate case-finding protocols. For medical specialists, it may be important to consider involving other experts in the treatment, such as other medical specialists, geriatricians, psychiatrists, district nurses and social workers. Optimal coordination among health care professionals is essential. Most of these principles are followed in geriatry and general practice; they might get a broader acceptance.

Some of the aspects of health care might be considered as indicators for quality of care, such as complications of treatment, readmissions, treatment strategies and compliance to generally accepted clinical guidelines. Our findings may suggest that patients who have a comorbid disease receive care of a lower quality. This issue of quality of care needs to be examined in greater detail, because most studies were retrospective and comorbid diseases were recorded from medial charts or a medical registration, instead of systematically examining the patients, and this could have introduced some bias. Uniform criteria for patient examination may contribute new information in this area. Second, standard therapy may be contraindicated in patients with comorbidity or there may be other valid reasons to refrain from it. Unfortunately, there is very little standard information about appropriate care for people with comorbid conditions. Therefore, we recommend that patients with comorbid conditions be included in clinical trials, assuming, of course, that their safety can be assured. We furthermore recommend that a new set of studies be conducted to examine continuity of care and patient satisfaction; important topics because patients with more than one disease are likely to be treated by several health care workers. Together, those studies will serve as the bases for a new generation of patient guidelines to meet the needs of growing older population in the 21st century.

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TABLES

Table 1
Characteristics of selected studies about causes of comorbidity

Reference No.	Author, year of publication	Index–disease	Setting	Method	*N*	Age (mean or range)	Comorbidity[a]	Results
12	Ottman & Lipton, 1994	epilepsy	sample of patients in a region	cross-sectional	1,948	36	pair (migraine)	Epilepsy (especially some subtypes) is a risk factor for migraine
13	Ottman & Lipton, 1996	epilepsy	sample of patients in a region	cross-sectional	1,405	36	pair (migraine)	There is no shared genetic susceptibility to both diseases
14	Peroutka, 1997	migraine	selection of referred patients	cross-sectional	137	50	pairs (arthritis, hypertension, ischaemic heart disease)	There is no shared pathophysiological variation in the C3 gene
15	Perna, 1997	asthma	allergology clinic	cross-sectional	51	31	pair (panic disorder)	Asthma induces the expression of an underlying vulnerability for panic disorder

[a]Comorbidity citation: pairs = index-disease with specific other disease versus only index-disease.

Table 3
Number of studies by outcome and index-disease

	Outcome						
			Health care				
Index-diseases	Mortality	FS/QoL[a]	Utilization	Treatment strategy	Complications of treatment	Discharge destination or readmission	Total
Cancers	9	3	2	6	0	0	19[b]
Diabetes mellitus	3	4	1	0	1	1	9[b]
Central nervous system diseases	0	1	0	0	0	0	1
Cardiovascular diseases	21	8	4	3	4	4	39[b]
Obstructive lung diseases	1	2	1	0	1	0	5
Musculoskeletal diseases	1	7	3	0	1	0	11[b]
Total	35	24[c]	8	9	5[c]	5	78[b,c]

[a]FS/QoL = functional status or quality of life.
[b]Some studies have more than one outcome variable.
[c]Some studies have more than one disease as index-disease.

Table 4
Number of studies by outcome and setting

	Outcome						
			Health care				
Setting	Mortality	FS/Qol	Utilization	Treatment strategy	Complications of treatment	Discharge destination or readmission	Total
General population	0	5	1	0	0	0	6
All or a random sample of patients with the index-disease in a certain region	6	2	2	6	0	0	16
Selected patients with the index-disease in a certain region	10	4	2	0	1	3	17[a]
General Practice population	0	1	0	0	0	0	1
One or several hospitals/outpatient clinics/pharmacies	19	11	2	3	4	2	37[a]
Rehabilitation center	0	1	1	0	0	0	1[a]
Total	35	24	8	9	5	5	78

[a]Some studies have more than one outcome variable.

Table 2
Characteristics of selected studies about consequences of comorbidity

Reference No.	Author, year of publication	Index-disease	Setting	Method	*N*	Age (mean or range)	Comorbidity[a]	Results[b]
Outcome:	Mortality							
16	Satariano & Ragland, 1994	breast cancer	all patients in a region	prospective	936	40–84	index	+
17	West et al., 1996	breast cancer	sample of all patients in a region	prospective	1,203	56	index	+
18	Newschaffer et al., 1997	breast cancer	all patients in a region	retrospective	404	>66	index	+
19	Koperna et al., 1997	colon cancer	hospital	retrospective	99	82	pairs	+/0
20	Liu, 1997	colon cancer	hospital	retrospective	68	66	not indicated	0
21	Payne & Meyer, 1997	colorectal cancer	hospital	retrospective	207	75	pair	+
22	Zincke et al., 1994	prostate cancer	hospital	retrospective	114	64	index	0
23	Albertsen et al., 1996	prostate cancer	all patients in a region	retrospective	451	65–75	index	+
24	Fowler et al., 1996	prostate cancer	hospital	retrospective	276	66	index	+
25	Marcelli et al., 1995	diabetes mellitus	selected patients in a region	retrospective	731	⩾25 pairs	+	
26	Medina et al., 1996	diabetes mellitus	selected patients in a region	prospective	584	59	pairs	+/0
27	Lavery et al., 1997	diabetes mellitus	selected patients in a region	retrospective	1,043	65	pairs	+/0
28	Fava et al., 1993	myocardial infarction	hospital	cohort	392	67	pair	+
29	Svensson LG, 1996	myocardial infarction	hospital	prospective	338	66	pairs	+/0
30	Capewell S, 1996	myocardial infarction	all patients in a region	retrospective	40,371	not indicated	pairs	+
31	Juszczak & Boyd, 1997							
32	Mickelson, 1997	myocardial infarction	hospital	retrospective	353	63	pair, count	pair: +, count: +
33	Localio, 1997	ischaemic heart disease	selected patients in a region	retrospective	12,266	not indicated	pairs	+
34	D'Hoore et al., 1996	ischaemic heart disease	selected patients in a region	retrospective	33,940	63	index	+
35	Ghali, 1996	ischaemic heart disease	selected patients in a region	retrospective	13,117	65	index	+
36	Flameng, 1996	ischaemic heart disease	hospital	prospective	741	65	pairs	+/0
37	Sergeant, 1997	ischaemic heart disease	hospital	retrospective	9,600	49	pairs	+/0
38	D'Hoore et al., 1993	ischaemic heart disease, heart failure, stroke	selected patients in a region	retrospective	62,456	64	index	+
39	Chin & Goldman, 1997	heart failure	hospital	prospective	257	67	pair, index	pair: +, index: +
40	Davis et al., 1995	stroke	hospital	retrospective	608	adults	pairs	0
41	Lai et al., 1995	stroke	all patients in a region	prospective	662	72	pairs	+/0
42	Stukenborg, 1997	stroke	selected patients in a region	retrospective	41,493	>65	index	+
43	Evans et al., 1994	transient ischaemic attack	several hospitals	prospective	330	not indicated	pairs	+/0
44	Panneton et al., 1995	aneurysm of abdominal aorta	hospital	retrospective	112	72	pairs	0
45	Halpern, 1997	aneurysm of abdominal aorta	hospital	retrospective	96	73	pairs	0
46	Katz et al., 1995	aneurysm of abdominal aorta	selected patients in a region	retrospective	10,014	70	pairs, count	pairs: +/0, count: +
47	Steyerberg et al., 1995	aneurysm of abdominal aorta	hospital	retrospective	238	not indicated	pairs	+
48	Feinglas, 1995	aneurysm of abdominal aorta	selected patients in a region	prospective	280	66	pairs	+/0
49	Von Kemp, 1997	peripheral vascular disease	hospital	prospective	200	67	pair	+
50	Antonelli Incalzi, 1997	COPD[c]	hospital	prospective	270	67	pairs, index	pairs: +/0, index: 0
51	Pincus et al., 1994	rheumatoid arthritis	hospital	prospective	75	55	pair	0
Outcome:	Functional status or quality of life							
52	Lindsey et al., 1995	breast cancer	several hospitals	prospective	19	appr. 70	pairs	0
52	Lindsey et al., 1995	lung cancer	several hospitals	prospective	26	appr. 70	pairs	0
53	Schag et al., 1994	lung cancer	several hospitals	cross-sectional	57	62	index	0
53	Schag et al., 1994	colon cancer	several hospitals	cross-sectional	117	65	index	0
53	Schag et al., 1994	prostate cancer	several hospitals	cross-sectional	104	70	index	+
54	Kurz et al., 1993	cancer	sample of all patients in a region	prospective	160	24–81	count	+ (only <60 years)

(*continued*)

Table 2
Continued

Reference No.	Author, year of publication	Index-disease	Setting	Method	*N*	Age (mean or range)	Comorbidity[a]	Results[b]
55	Johnson et al., 1996	diabetes mellitus (type II)	pharmacy	cross-sectional	54	51	count	+/0
56	Glasgow et al., 1997	diabetes mellitus	selected patients	cross-sectional	2,056	59	count	+
57	Jacobson et al., 1997	diabetes mellitus	outpatient center	cross-sectional	240	>18	pairs	+
58	Kuhn et al., 1996	Parkinson's disease	hospital	cross-sectional	54	62	pair	+/0
59	Sherbourne et al., 1996	diabetes mellitus	general practice	prospective	265	not indicated	pairs	+
59	Sherbourne et al., 1996	heart disease	general practice	prospective	131	not indicated	pairs	+/0
60	Chen, 1996	angina pectoris	hospital	cross-sectional	55	68	index	+
61	Kwa et al., 1996	ischaemic stroke	hospital	prospective	129	63	pairs	0
62	King, 1996	stroke	two hospitals	cross-sectional	86	63	pairs	+/0
63	Liu et al., 1997	stroke	rehabilitation center	cross-sectional	106	57	index	+
64	Nakayama et al., 1997	stroke	all patients in a region	cross-sectional	935	75	pairs	+/0
65	Ween et al., 1996	stroke	hospital	prospective	376	73	pairs, index	pairs: 0, index: +
66	Feinglass et al., 1996	claudication intermittent	selected patients in a region	cross-sectional	555	69	pairs	+/0
67	Bussing et al., 1995	asthma	general population	cross-sectional	551	5–17	count	+
68	Ferrer et al., 1997	COPDC	four hospitals and one prim. care center	cross-sectional	321	65	count	+
69	Hopman-Rock et al., 1997	rheumatic disease	general population	cross-sectional	186	66	pair	+/0
70	Schaardenburg et al., 1995	musculoskeletal disorders	general population	cross-sectional	105	85–100	pairs	+/0
71	Katz & Yelin, 1993	rheumatoid arthritis	selected patients in a region	cross-sectional	2,231	55	pair	+
72	Belza et al., 1993	rheumatoid arthritis	research center	cross-sectional	133	67	count	+
73	Talamo et al., 1997	rheumatoid arthritis	outpatient clinic	cross-sectional	137	62	count	+
74	Verbrugge, 1995	osteoarthritis	general population	cross-sectional	?	not indicated	pairs, count	pairs: +/0, count: +
75	Ettinger et al., 1994	knee osteoarthritis	general population	prospective	217	45–74	pairs	+/0
Outcome:	Health care: utilization							
76	Taplin et al., 1995	colon, prostate, breast cancer	all patients in a region	retrospective	6,129	≥35	index	+
77	Shwartz et al., 1996	Lung cancer, prostate cancer, myocardial infarction, ischaemic heart disease, stroke, COPDC, asthma	selected patients in a region	retrospective	4,439	≥18	index	+
11	Gilmer et al., 1997	diabetes mellitus	all patients in a region	retrospective	3,017	60	pairs	+/0
78	Matsui et al., 1996	suspected myocardial infarction	hospital	prospective	1,261	61	index	+
79	Monane et al., 1996	ischaemic stroke	hospital	retrospective	645	74	index	+
63	Liu et al., 1997	stroke	rehabilitation center	cross-sectional	106	57	index	+
71	Katz & Yelin, 1993	rheumatoid arthritis	selected patients in a region	retrospective	2,231	55	pair	+/0
80	Ward & Rao, 1995	rheumatoid arthritis	selected patients in a region	prospective	161	54	dichotomy	+
Outcome:	Health care: treatment strategy							
81	Smith et al., 1995	lung cancer	all patients in a region	cross-sectional	4,999	≥65	index	+
82	August et al., 1994	breast cancer	hospital	cross-sectional	128	55–64	count	+
83	Nicolucci et al., 1993	breast cancer	all patients in a region	cross-sectional	1,724	61	index	+
84	Newschaffer et al., 1996	breast cancer	all patients in a region	cross-sectional	2,216	≥66	index	+

(*continued on next page*)

Table 2
Continued

Reference No.	Author, year of publication	Index-disease	Setting	Method	*N*	Age (mean or range)	Comorbidity[a]	Results[b]
85	Hillner et al., 1996	breast cancer	all patients in a region	cross-sectional	3,361	≥65	index	0
19	Koperna et al., 1997	colon cancer	hospital	cross-sectional	99	82	index	+
86	Krumholz et al., 1995	myocardial infarction	all patients in a region	cross-sectional	10,018	≥65	pairs	+
87	McLaughlin et al., 1997	myocardial infarction	all patients in a region	cross-sectional	2,409	not indicated	index	+
32	Mickelson et al., 1997	myocardial infarction	sample of all patients in a region	cross-sectional	353	63	pair, index	pair: +, index: +
Outcome:	Health care: complications of treatment							
88	Geraci et al., 1995	diabetes mellitus	hospital	retrospective	554	66	pairs	+/0
88	Geraci et al., 1995	heart failure	hospital	retrospective	837	65	pairs	+/0
88	Geraci et al., 1995	COPDC	hospital	retrospective	446	60	pairs	+/0
89	Ryan et al., 1997	ischaemic heart disease	hospital	retrospective	111	not indicated	pairs	+/0
90	Rigdon et al., 1997	stroke	hospital	retrospective	237	63	pairs	+/0
91	Piotrowski et al., 1996	abdominal aortic aneurysm	hospital	retrospective	71	71	pairs	0
92	Kaandorp et al., 1995	joint disease	selected patients in a region	prospective	4,907	>18	pairs	+/0
Outcome:	Health care: discharge disposition or readmissions							
27	Lavery et al., 1997	diabetes mellitus	selected patients in a region	retrospective	1,043	65	index	+/0
39	Chin & Goldman, 1997	heart failure	hospital	prospective	257	67	pair, index	pair: o, index: +
93	Krumholz et al., 1997	heart failure	selected patients in a region	retrospective	17,448	≥65	index	+
42	Stukenborg, 1997	stroke	selected patients in a region	retrospective	41,493	>65	index	0
65	Ween et al., 1996	stroke	hospital	prospective	376	73	pairs, index	pairs: 0, index: 0

[a]Comorbidity citation: index = comorbidity index, count = comorbidity count, pairs = index disease with specific other disease versus only index disease, dichotomy = comorbidity versus no comorbidity.

[b]Results: + = comorbidity is associated with outcome, 0 = comorbidity is not associated with outcome, +/0 = some of the comorbid diseases are associated with outcome, or for some of the dimensions of outcome.

[c]COPD = chronic obstructive pulmonary disease.

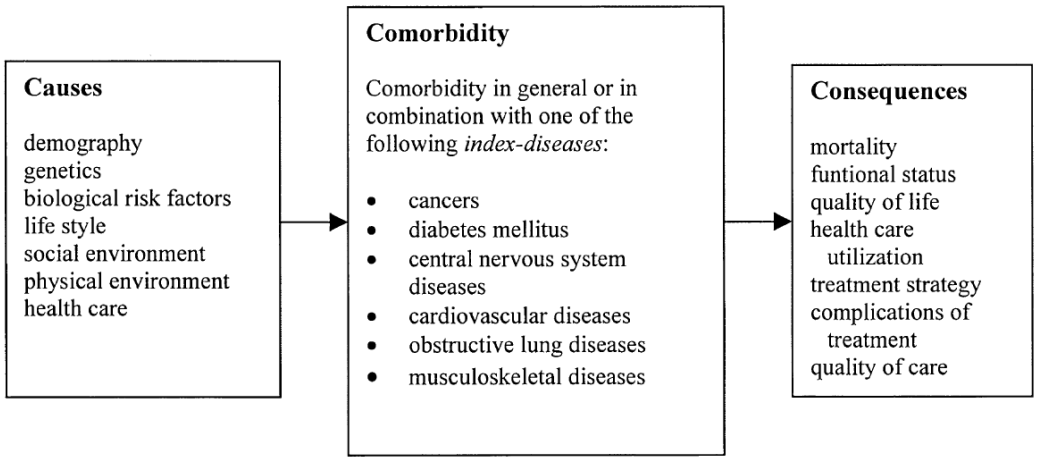

Fig. 1. Conceptual model describing comorbidity and its causes and consequences.

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