



# Physiological markers and multimorbidity: A systematic review

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## Abstract

**Background:** Multimorbidity is the co-occurrence of two or more diseases in the same individual. One method to identify this condition at an early stage is the use of specific markers for various combinations of morbidities. Nonetheless, evidence related to physiological markers in multimorbidity is limited. **Objective:** The aim was to perform a systematic review to identify physiological markers associated with multimorbidity. **Design:** Articles available on PubMed, Register of Controlled Trials, Academic Search Premier, CINAHL, Scopus, SocINDEX, Web of Science, LILACS, and SciELO, from their inception to May 2018, were systematically searched and reviewed. The project was registered in PROSPERO under the number CRD4201705522. **Results:** The systematic search identified 922 papers. After evaluation, 18 articles were included in the full review reporting at least one physiological marker in coexisting diseases or which are strongly associated with the presence of multimorbidity in the future. Only five of these studies examined multimorbidity in general, identifying five physiological markers associated with multimorbidity, namely, dehydroepiandrosterone sulfate (DHEAS), interleukin 6 (IL-6), C-reactive protein (CRP), lipoprotein (Lp), and cystatin C (Cyst-C). **Conclusions:** There is a paucity of studies related to physiological markers in multimorbidity. DHEAS, IL-6, CRP, Lp, and Cyst-C could be the initial focus for further investigation of physiological markers related to multimorbidity.

## Keywords

Multimorbidity, physiological markers, comorbidity, molecular markers

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## Introduction

Multimorbidity is the co-occurrence of two or more diseases in the same individual, which are often associated with each other.<sup>1,2</sup> It is more common in elderly,<sup>3</sup> and it affects one in five adults and two-thirds of the elderly.<sup>4,5</sup> Multimorbidity is more prevalent in groups from lower socioeconomic status.<sup>4</sup> Although studies about multimorbidity have recently begun, evidence has already shown that it leads to a decrease in quality of life,<sup>6</sup> functional decline,<sup>7</sup> and an increased risk of mortality,<sup>8</sup> in addition to difficulty to manage it adequately. Early diagnosis and management of multimorbidity may be important factors to minimize serious consequences. One method to identify this condition at an early stage is the use of specific physiological and molecular markers for various combinations of morbidities.<sup>9</sup>

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Some attempts have been made to identify physiological markers associated with multimorbidity. Reviews have evaluated markers that are associated with pairs of diseases. For example, high levels of B-type natriuretic peptide are commonly associated with dyspnea and have prognostic value in the acute coronary syndromes, such as myocardial infarction, diastolic dysfunction, and atrial fibrillation in congestive heart failure patients.<sup>10</sup> Cancer patients frequently have obesity and diabetes as comorbidity conditions. Current studies show that microRNAs such as miR-9 may serve as novel biomarkers and molecular targets for cancer therapy in patients with comorbidity conditions.<sup>11</sup>

Recently, other alternatives have been attempted to improve early detection of multimorbidity. Alemi et al. developed the multimorbidity index to account for the prognosis of patients with multiple diagnoses. The authors have reported that physiological markers may help not only in the prevention of certain conditions and comorbidities but also in the possibility of early diagnosis and treatment, increasing the chances of survival of patients and decreasing health expenditures.<sup>12,13</sup>

Using simple blood tests in hospital and/or outpatient laboratories may be an easy-to-access alternative for the population to detect specific physiological markers for a set of diseases. As there are few studies evaluating markers related to multiple concomitant diseases, the aim of this article is to perform a systematic review to identify physiological markers associated with multimorbidity.

## Materials and methods

The search was conducted in the following electronic databases: MEDLINE (via PubMed), Register of Controlled Trials (Cochrane CENTRAL), Academic Search Premier, CINAHL, Scopus, SocINDEX, Web of Science, LILACS, and SciELO. The search was conducted in the first semester of 2018 and included all articles from the beginning of the bases until May 2018. Manuscripts written in the following languages were included, English, Portuguese, or Spanish. The Medical Subject Headings (MeSH) terms and their synonyms were used to search the terms in all fields. The search strategy used in PubMed is shown in Table 1.

The systematic review was reported according to the PRISMA statement and the AMSTAR 2.<sup>14,15</sup> According to PICOS principles,<sup>14</sup> we consider the following criteria: P means any patient who presented multimorbidity; I means patients with multimorbidity (who have two or more coexisting diseases); C stands for patients who have none or one disease; O means any physiological or molecular marker; and S stands for the study design, mainly observational/epidemiological studies.

Observational studies, which evaluated molecular, physiological, or genetic markers related to different multimorbidity, were selected. The inclusion criteria were studies reporting specific markers to a condition of at least two concomitant diseases. The exclusion criteria were papers

**Table 1.** Literature search strategy used for the PubMed database.

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#1	“multimorbidity”[MeSH] OR “comorbidity” OR “comorbidity” OR “multicomorbidity” OR “multi-morbidity” OR “-morbidity” OR “-morbid conditions” OR “multiple diseases” OR “multiple morbidities” OR “multimorbid” OR “multiple pathology” OR “disease clustering” OR “chronic diseases” OR “Severity of Illness Index”
#2	“physiological markers” OR “Markers, Biological” OR “molecular markers” OR “Biology, Molecular” OR “Genetics, Molecular” OR “Molecular Genetic” OR “Biochemical markers”
#3	#1 AND #2

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that did not specify the marker or were related to one specific disease; studies evaluating seasonal or allergic diseases, general markers of oxidative stress, or markers of resting metabolic rate; and reviews or papers in a language other than English, Spanish, or Portuguese. Full texts of the selected articles after screening the titles and abstracts were assessed, and data were extracted using predetermined formats. The extracted data included author(s) and year of the publication, type of the study, sample, morbidities, and the evaluated biomarkers.

Two independent researchers (GDF and JAS) performed the literature search, screening titles and abstracts, full-paper reviews, study quality assessment, and data extraction. Disagreements were referred to a third author.

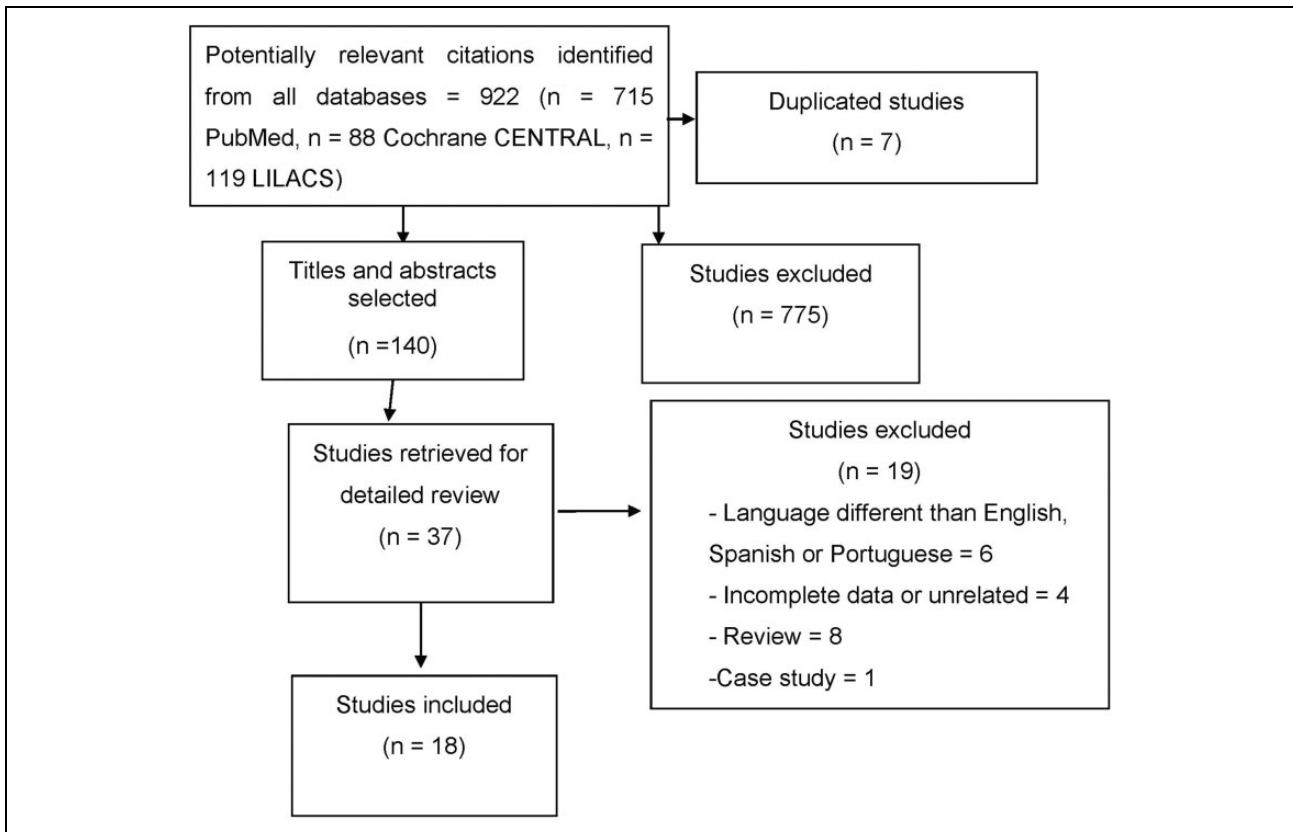
The project was registered in PROSPERO under number CRD42017055522.

## Results

The search identified 922 papers. We found seven duplicate studies and another 775 were excluded as they did not include the outcome of interest. Thereafter, 140 papers were screened to title and abstract selection, and 37 papers were selected for full-text evaluation. Nineteen papers were excluded for the following reasons: languages other than English, Spanish, or Portuguese; literature review, case study, or incomplete data. In the end, 18 papers reporting at least one physiological marker with coexisting diseases were included in the systematic review (Figure 1).

Tables 2 and 3 show the characteristics of the included studies.

In relation to disease conditions, the studies are heterogeneous, and only five evaluated multimorbidity in a more widespread construct (Table 2). Although only five studies dealt exclusively with multimorbidity in general, our search selected some studies, which associated markers for specific comorbidities. We only considered papers evaluating at least two of the following diseases related to different markers: three studies related renal and cardiovascular disease, two studies with behavioral diseases, two with bone diseases associated with periodontal diseases and Alzheimer, one study related to depression and



**Figure 1.** The flow diagram of studies included in the review.

hypertension, one related to different cardiac conditions, one related to psoriasis and metabolic comorbidities, one study about infectious diseases, and two studies with healthy people that evaluated markers predicting multimorbidity (Table 3).

## Discussion

This article aims to review the literature to identify physiological markers associated with patterns of multimorbidity. Based on the systematic search, we found 18 studies from 2004 to 2017, which evaluated physiological markers related to different concomitant diseases or which are strongly associated with the presence of multimorbidity in the future.

No randomized clinical trials (RCTs) were found in the search strategy, most part of the studies carried out observational analyses, and none cited a methodology including blind review. Nevertheless, from the 18 included studies, 15 presented a control group for comparability: patients who had only one of the morbidities of the study<sup>16–24,27,28,30,33</sup> or without morbidity (matched according to sex and age).<sup>19,26,29</sup> Although all included papers assessed association between at least two different morbidities, only five assessed specifically markers for multimorbidity in general regardless of the disease. The three studies, which did not present control groups, were related

to correlation between variables, which may increase the risk of comorbidities.<sup>25,31,32</sup> In general, even considering that the included papers are not RCT or long follow-up periods, the presence of a control group in most studies can be used to assist with a more thorough data analysis. Nevertheless, suggestions are put forward as the results are not conclusive, because the aim is to observe cross-sectional data. The quality evaluation of the studies followed the parameters of the Newcastle–Ottawa scale.<sup>34</sup>

### Physiological markers and multimorbidity

Only five studies evaluated multimorbidity in general. The results cross-sectional data show that the elevated interleukin 6 (IL-6) and lower dehydroepiandrosterone sulfate (DHEAS) are associated with a greater burden of multimorbidity and suggest that investing in these markers may be an alternative for earlier detection and target interventions aimed at reducing multimorbidity.<sup>16</sup> Although high levels of serum cytokines such as IL-6 and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) are considered risk factors for several chronic diseases, the second study emphasizes that these markers are not available in the majority of clinical laboratories. Therefore, other markers should be studied, such as C-reactive protein (CRP), lipoprotein (Lp), and cystatin C (Cyst-C) levels. People in the group of those with zero or one disease showed normal levels for the markers, as the

**Table 2.** Characteristics of the included studies that analyzed multimorbidity.

First author, year, country	Design	Sample	n	Measured biomarkers	Conclusions
Fabbi, 2015, Italy <sup>16</sup>	Cohort	Aged 60 years or older	1018 participants (InCHIANTI Study)	Inflammatory IL-6 and anabolic hormonal (DHEAS) biomarkers associated with multimorbidity that was evaluated at baseline and follow-up visits as number of diagnosed diseases from a predefined list of 15 candidate chronic condition.	Higher IL-6 and lower DHEAS was associated with higher number of diseases, independent of age, sex, body mass index, and education. 0 = no disease (n = 213) 1 = one disease (n = 347) 2, 3 = two or three diseases (n = 364) 4+ = four or more diseases (n = 94). • IL-6 (pg/mL), median (IQR): 0 = 2.3 (1.8–3.4), 1 = 2.7 (1.9–3.6), 2, 3 = 3.0 (2.0–4.1), 4+ = 3.9 (2.8–5.1), p < 0.001. • DHEAS ( $\mu$ g/dL), median (IQR): 0 = 84.2 (49.6–142.4), 1 = 71.1 (43.3–115.4), 2, 3 = 58.8 (32.8–104.5), 4+ = 54.6 (33.5–89.3), p < 0.001
Garrafa, 2017, Italy <sup>17</sup>	Cohort	Older persons	134 (60% women) (mean age was 77.7 $\pm$ 7.6 years). (ANZIANI IN-RETE study, a prospective population-based study)	CRP, Lp, and Cyst-C	Reference values suggested by the literature: Lp < 0.3 g/L, Cyst-C value < 1.11 mg/L and CRP < 5 mg/L. Higher levels of the markers were associated with higher number of diseases. Groups: Number of Chronic Disease 0/1, 2/3, 4, or more. (%) Percentage of person with normal value of markers. CRP: 0/1 = 92.9%, 2/3 = 82.2%, 4+ = 65.3%. Lp: 0/1 = 85.7%, 2/3 = 86.4%, 4+ = 60.3%. Cyst C: 0/1 = 91.7%, 2/3 = 61.5%, 4+ = 43.1%. Having two or more chronic conditions was positively associated with increased of the inflammation factor by 0.22 units (p < 0.001), mainly related to IL-6 and CRP. Having two or more chronic conditions is related to a higher concentration (mg/dL) of CRP (p < 0.001). Two or more chronic diseases = 0.580 $\pm$ 0.012. One chronic disease = 0.392 $\pm$ 0.011. Healthy controls = 0.265 $\pm$ 0.011. After adjusted for age and sex, the higher the concentration of CRP (mg/L) is associated (OR (95% CI)) with multimorbidity. CRP $\leq$ 3 = reference. CRP 3 to < 10 = 1.62 (1.21; 2.19). CRP $\geq$ 10 = 2.84 (1.83; 4.40).
Friedman, 2015, USA <sup>18</sup>	Cohort	Older persons	1255 participants (MIDUS study)	IL-6, CRP, fibrinogen	
Stapanova, 2015, USA <sup>19</sup>	Cross-sectional	Adults persons	26,225 participants (NHANES study), of these 9992 had two or more chronic diseases (average of chronic diseases was 3.017 $\pm$ 0.021).	C-reactive protein	
Schöttker, 2016, Germany <sup>20</sup>	Cohort	Adults and older persons (aged 50–74 years)	2547 participants (51.9% women) (median age was 70 years). Multimorbidity assessed by the Cumulative Illness Rating Scale–Geriatric version	CRP	

IL-6: interleukin 6; DHEAS: dehydroepiandrosterone sulfate; IQR: interquartile range; CRP: C-reactive protein; Lp: lipoprotein; Cyst-C: cystatin C levels; OR: odds ratio; CI: confidence interval.

**Table 3.** Characteristics of the included studies that analyzed at least two coexisting diseases (comorbidities).

First author, year, country	Design	Sample	n	Measured biomarkers	Conclusions
Gabr, 2004, Saudi Arabia <sup>21</sup>	Cross-sectional	IHD and diabetes in ESRD patients on chronic HD.	73 patients (40 female) divided into 4 groups: 20 patients with IHD, 17 patients with diabetes, 19 patients with diabetes and IHD, and 17 patients without evidence of myocardial damage.	cTnT	53% of diabetic and 37% of IHD patients had an increased cTnT; 59% of IHD and diabetic patients had an increased cTnT and 29% of noncardiac disease patients had an increased cTnT. In dialyzed patients, cTnT ( $\mu\text{g/L}$ ) without IHD is 0.04 and with IHD is 0.15. ( $p < 0.05$ ).
Onyenekwe, 2008, Nigeria <sup>22</sup>	Cross-sectional	Malaria and HIV coinfection	Malaria and HIV coinfection group ( $n = 45$ ) and HIV infected group without concurrent malaria infection ( $n = 57$ )	Serum iron and albumin concentrations	Serum iron decreased and albumin increased in (1) Malaria-HIV coinfection group compared with (2) HIV infection group. Iron: (1) $107.5 (\pm 53.5) \times (2) 151.9 (\pm 79.3)$ Albumin: (1) $42 (\pm 9.6) \times (2) 38.4 (\pm 7.5)$
Zhou, 2008, UK <sup>23</sup>	Cross-sectional	ADHD and CD comorbidity	141 ADHD + CD and 435 ADHD - CD	Genotypes of 20 DAT1 markers were analyzed. 51 candidate genes in which the association with DAT1	Heterogeneity test found the two SNP (rs40184, rs2652511) with significant transmission pattern difference between ADHD + CD and ADHD - CD children ( $p = 0.016$ ), indicating that DAT1 has a significantly greater genetic influence on ADHD with than without CD.
Luckhaus, 2009, Germany <sup>24</sup>	Case-control	To detect comorbidity with Op at a subclinical level were studied concentrations of biochemical Op markers in subjects with MCI and mild AD compared to subjects with primary Op and age-matched cognitively normal controls	Control = 8, Op = 7, MCI = 19 AD = 20	C-terminal collagen fragments (marking bone catabolism), Osteocalcin (marking bone remodeling and anabolism)	Equally increased C-terminal collagen in Op and AD (+68%) versus controls. Osteocalcin was concomitantly increased in Op (+63%) and in AD (+76%) versus controls. These results point to increased bone catabolism and concomitant remodeling in mild AD but not in cognitive impairment, associating the comorbidity of AD with Op in the early disease course.
Conroy, 2011, USA <sup>25</sup>	Cross-sectional	Mid-adolescents	106 school children (65 males), 11-15 years	RBP4 correlated with metabolic (lipids, glucose), and inflammatory (TNF- $\alpha$ , IL-6, CRP, adiponectin) markers for adiposity and alanine ALT.	Circulating concentrations of RBP4 are correlated with multiple risk factors for adiposity-related comorbidities. Serum RBP4 was significantly correlated with ALT and triglycerides and inversely correlated with adiponectin. RBP4 is a marker that may offer preventive measures in those who are at increasing risk for comorbidities.

(continued)

Table 3. (continued)

First author, year, country	Design	Sample	n	Measured biomarkers	Conclusions
Jabbar, 2011, UK <sup>26</sup>	Case-control	Periodontal disease in postmenopausal women with and without Op	185 postmenopausal Op women and 185 age- and sex-matched control	Plasma cytokines: vitamin D, bone mineral density, OPG and RANKL.	Higher proportion of the women with Op had periodontal disease compared with control (87.6% vs. 37.8%, $p < 0.001$ ). Plasma vitD was lower, and RANKL ( $0.66 \pm 0.67$ vs. $0.37 \pm 0.38$ ) and OPG ( $18.70 \pm 9.70$ vs. $10.44 \pm 5.85$ ) were significantly higher in the women with Op than in control. CRP (ng/L) was higher in patients ( $6.42 \pm 7.72$ ) than in control ( $4.03 \pm 4.24$ ).
Taurines, 2011, Germany <sup>27</sup>	Case-control	Children and adolescents with ADHD and ASD: highly comorbid with ADHD	ADHD ( $n = 51$ ) and ASD ( $n = 26$ ), diagnosed according to ICD-10 criteria as well as healthy controls ( $n = 39$ )	mRNA expression of monoaminergic candidate genes (DRD4, DRD5)	The concentrations of DRD4 in the blood were significantly lower in ADHD and ASD children (19 of 26 comorbid with ADHD) compared to healthy controls ( $p = 0.005$ ). Just ASD patients revealed a significantly decreased DRD5 mRNA expression in comparison to the two other groups ( $p = 0.001$ ). mRNA expression may be useful tools in (differential) diagnostic procedures of ADHD with or without ASD.
Adamczyk, 2012, Poland <sup>28</sup>	Cross-sectional	Degenerative AS in relation to the AVCS and concomitant CAD	88 patients: 68 patients with degenerative AS (group A), including 44 patients with severe AS (A1; 25 patients with CAD) and 24 patients with moderate AS (A2; 13 patients with CAD), and 20 matched subjects as controls (18 patients with CAD)	Markers of calcification: OPG	In moderate AS, serum OPG levels were higher in subjects with concomitant CAD versus without CAD ( $5.84 \pm 1.4$ vs. $4.03 \pm 1.3$ pmol/L, $p = 0.036$ ).
AlMutairi, 2013, Kuwait <sup>29</sup>	Case-control	Psoriasis and comorbidities (diabetes, obesity, heart disease, hypertension, and metabolic syndrome).	100 patients (71 male) with stable plaque psoriasis (psoriasis area and severity index $\geq 10$ ), compared with equal number of matched healthy volunteers	Cathelicidin (LL-37), and vitamin D in psoriasis patients with comorbidities	Reference values for comorbidities: hypertension (BP $\geq 140/90$ mmHg), diabetes (fasting blood sugar $> 125$ mg%), dyslipidemia (triglyceride $\geq 150$ mg%, and/or LDL $\geq 160$ mg%), obesity (BMI $> 30$ kg/m <sup>2</sup> ). Metabolic syndrome was diagnosed in the presence of three or more criteria of the National Cholesterol Education Program's Adult treatment Panel III. The vitamin D levels were lower in patients with psoriasis and comorbidities ( $29.53$ nmol/L $\pm 9.38$ nmol/L vs. $53.5$ nmol/L $\pm 19.6$ nmol/L). Furthermore, the levels of serum LL-37 were significantly high ( $18.16$ ng/mL vs. $7.92$ ng/mL).

(continued)

**Table 3.** (continued)

First author, year, country	Design	Sample	n	Measured biomarkers	Conclusions
Patange, 2013, USA <sup>30</sup>	Case-control	Pediatric patients with CKD and comorbidity cardiovascular disease	34 children with CKD (no history of cardiac disease congenital or structural). The control group consisted of 33 age- and sex-matched children free of any underlying cardiac or renal disease	Parameters of vitamin D and cardiovascular structure (LVMI)	LVMI was correlated with vitamin D ( $r = -0.54$ ; $p = 0.05$ ). Cases (CKD) versus reference range: vitamin D (ng/dL): $18.79 \pm 9.95$ versus $30-100$ ng/dL. Comparing dialysis ( $n = 20$ ) versus nondialysis ( $n = 14$ ) = LVMI $46.94 \pm 12.12$ versus $35.68 \pm 10.57$ . CKD more severe high the risk of cardiovascular disease.
Felipe, 2015, Chile <sup>31</sup>	Cross-sectional	Presumed healthy men	66	Serum ferritin: association between hyperferritinemia and metabolic syndrome parameters	There are correlations between serum ferritin and metabolic syndrome parameters (HDL cholesterol $r = -0.285$ , triglycerides $r = 0.388$ , and fasting glucose $r = 0.481$ ). There is an increase of the serum ferritin with the quantity of RF of metabolic syndrome. Zero RF = 152.8 and three or more RF = 286.2. Besides that oxidative stress markers, hepatic damage markers (GGT, SGOT), and HOMA index were correlated with serum ferritin.
Sinha, 2015, UK <sup>32</sup>	Cohort	Children with non-dialysis stages 3-5 of CKD	83 children (51 boys; mean age $12.1 \pm 3.2$ years) with a mean estimated GFR of $32.3 \pm 14.6$ mL/min	Serum intact FGF23 with indexed LVMI	CKD-associated mineral bone disease is a significant factor contributing to the increased cardiovascular risk in patients with CKD. Was observed no significant relationship of FGF23 with LVMI ( $r = 0.16$ , $p = 0.15$ ). Cannot clarify the roles of FGF23 with LV mass and their roles in the evolution of the development of adverse cardiovascular outcomes.
Robaczewska, 2016, Poland <sup>33</sup>	Case-control	Patients with depression, hypertension, or comorbid depression + hypertension and healthy age- and sex-matched controls	Four groups of patients aged 50 or more. $n = 15$ depression, $n = 20$ hypertension; $n = 16$ hypertension + depression; and $n = 19$ healthy age- and sex-matched controls	HO-1	HO-1 was decreased in patients with depression and was significantly associated with the severity of symptoms (decreased enzyme expression was correlated with increased severity of depressive). The relationship between HO-1 and the prevalence of depressive symptoms was confirmed by logistic regression, which allowed classification of hypertensive patients as depressed based on HO-1 concentrations ( $p < 0.01$ ). Decreased expression of HO-1 may contribute to the risk of depression in hypertension.

IHD: ischemic heart disease; ESRD: end-stage renal disease; HD: hemodialysis; cTnT: cardiac troponin T; ADHHD: attention deficit hyperactivity disorder; CD: conduct disorder; MCI: mild cognitive impairment; AD: Alzheimer's disease; Op: osteoporosis; RBP4: retinol-binding protein 4; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; IL-6: interleukin 6; CRP: C-reactive protein; ALT: aminotransferase; OPG: osteoprotegerin; ASD: autism spectrum disorders; AS: aortic stenosis; AVCS: aortic valve calcium score; CAD: coronary artery disease; CKD: chronic kidney disease; LVMI: left ventricular mass index; RF: risk factors; GFR: glomerular filtration rate; FGF23: fibroblast growth factor 23; HO-1: heme oxygenase; SNP: single nucleotide polymorphisms; HDL: high density lipoprotein; ICD: international classification of diseases; GGT: gamma glutamyl transferase; SGOT: serum glutamic oxalacetic transaminase; HOMA: homeostatic model assessment.

number of chronic diseases increased the percentage of a person with a normal value of the markers decreased, showing that they are markers which can also be considered for detection of multimorbidity.<sup>17</sup> Three other studies also suggested CRP as a possible marker for multimorbidity, associating the increase of its concentration with two or more chronic conditions.<sup>18–20</sup> These data should be analyzed with caution, because cross-sectional and longitudinal studies have limitations to identify cause or consequence.

### *Physiological markers, patterns of multimorbidity, and specific combinations of diseases*

In relation to the studies described in Table 3, combinations of pairs of diseases were normally controlled by individuals with only one of the associated diseases, thus observing the pattern of specific markers between groups. Three studies related renal and cardiovascular diseases. In ischemic heart disease (IHD) and diabetes in end-stage renal disease (ESRD) patients, it was observed that cardiac troponin T (cTnT) was increased in IHD and diabetic patients compared to control and isolated diseases, suggesting that increased cTnT appears to be the most specific biochemical marker to predict subclinical myocardial damage in ESRD patients.<sup>21</sup> It is suggested that chronic kidney disease severely increases the risk of cardiovascular disease<sup>30</sup>; however, it does not seem to be associated with mineral bone disease.<sup>32</sup>

Two studies analyzed attention deficit hyperactivity disorder (ADHD) and conduct disorder (CD) comorbidity. The genetic heterogeneity showed that variations in the dopamine active transporter 1 (DAT1) gene confer significantly different risks to ADHD children to either have or not have CD.<sup>23</sup> These data corroborate with Gizer who showed co-occurrence among psychiatric disorders and that the candidate gene studies of psychological disorders are involved in monoaminergic function (DAT1) giving the relevance of these neurotransmitter systems to brain-behavior relations.<sup>35</sup> Taurines et al. also related monoaminergic genes to comorbidities with autism spectrum disorders.<sup>27</sup>

One study reported different cardiac conditions and concluded that the presence of coronary artery disease in moderate aortic stenosis was associated with increased serum osteoprotegerin (OPG) levels, suggesting the effect of atherosclerosis on early valve calcification.<sup>28</sup> Moreover, one study evaluated depression and hypertension and showed that decreased expression of heme oxygenase may contribute to the risk of comorbidity of depression in hypertension cases.<sup>33</sup>

Two studies reported osteoporosis with comorbidities. It is clear that in Alzheimer's disease there is an increase in bone catabolism, associating the comorbidity of Alzheimer's disease with osteoporosis in the early disease course detected at the level of biochemical blood markers, such as C-terminal collagen fragments and osteocalcin.<sup>24</sup> Other comorbidity is periodontal disease, which is more common

in women with osteoporosis and is associated with lower vitamin D and higher concentrations of RANKL and OPG.<sup>26</sup>

Psoriasis and comorbidities (diabetes, obesity, heart disease, hypertension, and metabolic syndrome) can be evaluated with cathelicidin (LL-37) and vitamin D. Vitamin D levels were lower in patients with psoriasis and comorbidities, but serum LL-37 levels were significantly elevated.<sup>29</sup> Furthermore, one study analyzed the coinfection of malaria and HIV compared to HIV-infected individuals without concurrent malaria infection and showed that serum iron and albumin concentrations were indicators related with malaria infection in HIV-infected subjects.<sup>22</sup>

Two studies with healthy people evaluating markers that predict multimorbidity were included. In adolescents, the establishment of retinol-binding protein 4 as a marker may offer health-care providers a tool to begin aggressive preventive measures in those who are at increasing risk for adiposity-related comorbidities but have not yet been afflicted by them.<sup>25</sup> In healthy men, significant correlations were found between serum ferritin concentration and metabolic syndrome parameters.<sup>31</sup>

### *Related findings*

A birth cohort study aimed at assessing the association of obesity with physiological markers at 22 years of age, showing direct association for IL-6 and CRP and an inverse association for adiponectin, suggesting early care for this population at risk.<sup>36</sup> A meta-analysis of prospective studies suggests the association of IL-6 and CRP with type 2 diabetes risk (relative risk of 1.31 per 1 log pg/mL increment in IL-6 levels and of 1.26 per 1 log mg/L increment in CRP levels).<sup>37</sup>

Therefore, a systematic review has shown the elevation of the concentrations of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ) in metabolic syndrome, suggesting that the measurement of these biomarkers may aid in the detection of these disorders,<sup>38</sup> and agrees with findings from the past decade that have already indicated that laboratory-measured pro-inflammatory markers are needed to target specific treatment in the metabolic syndrome.<sup>39</sup>

### *Limitations*

As limitations of this study, the included papers were cross-sectional analyses; however, it is not clear whether the marker is a cause or a consequence related to different pairs of diseases. In addition, only five studies are performed with nonspecific concomitant diseases, showing the existing gap in the literature. Therefore, more studies controlling confounding variables and monitoring different conditions are needed to find markers that allow the prevention or early treatment of different multimorbidity.



## Conclusions

This study was important for grouping physiological markers associated with different types of comorbidities to facilitate early diagnosis and intervention in these patients. Nonetheless, there is a paucity of studies related to physiological markers and multimorbidity. In the initial efforts, despite cross-sectional analyses, DHEAS, IL-6, CRP, Lp, and Cyst-C seem to be the choices for further investigation regarding the effects of physiological markers related to multimorbidity.

## Authors' note

All authors have read and agreed the Statement for Authors.


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