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The possible role of physical activity in the modulation of gut microbiota in chronic kidney disease and its impact on cardiovascular risk: a narrative review

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Abstract. **Chronic degenerative non-communicable diseases (CDNCDs), in particular chronic kidney disease, induce gut microbiota (GM) dysbiosis, which, in turn, worsens the progression of CDNCDs and patients' quality of life. We analyzed literature studies to discuss the possible positive and beneficial impact of physical activity on GM composition and CV risk in CKD patients. Regular physical activity seems to be able to positively modulate the GM, reducing the systemic inflammation and consequently the production of uremic gut-derived toxins, which are directly correlated with the increase of cardiovascular risk. In particular, the accumulation of indoxyl sulphate (IS) seems to be able to induce vascular calcifications, vascular stiffness and cardiac calcifications, while p-Cresyl sulphate (p-CS) seems to be able to exert a cardiotoxic action through metabolic pathways, capable of inducing oxidative stress. In addition, trimethylamine N-oxide (TMAO) can alter lipid metabolism, inducing the production of foam cells and causing an accelerated atherosclerosis process. In this context, a regular physical activity program seems to represent an adjuvant non-pharmacological approach for the clinical management of CKD patients.**

Key Words:
Gut microbiota, Physical activity, Chronic kidney disease, TMAO, Indoxyl sulphate, p-Cresyl sulphate, Lifestyle, Microbiome.

Introduction

The human gut is colonized by a complex community consisting of more than 1,500 different species of microorganisms. This community, which includes bacteria, viruses and some eukaryotic species, is called microbiota[1]. The gut microbiota (GM) plays a pivotal role in protecting the host against pathogens, supports the immune system, exerts an important action in the digestive processes and synthesizes some molecules that are involved in maintaining the host's health state. In fact, GM could be considered a dynamic organ because it can be modified by several variables and its composition can be modulated during the host lifespan[2]. Numerous factors influence the GM composition, such as the delivery mode, feeding type, ethnicity, age, eating habits, lifestyle, physical activity (PA), the use of antibiotics, etc[3-7]. Moreover, GM composition can be altered by several pathological conditions, among these chronic degenerative non-communicable diseases (CDNCDs), that is cardiovascular (CV) disease, chronic kidney disease (CKD), diabetes mellitus, metabolic syndrome and cancer[8-11].

In physiological conditions, the main phyla" found in human microbiota are Bacteroidetes and Firmicutes, followed by Proteobacteria, Fusobacteria, Tenericutes, Actinobacteria, and Verru-

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comicrobia[1,12]. Recently, it has been hypothesized that a "healthy functional core" is present in the microbiota of healthy subjects and it seems to exert a series of metabolic and molecular functions that are not necessarily performed by the same bacterial species[13].

In CV disease patients, it was observed an alteration of GM composition, characterized by a decrease of the species producing butyrate, such as *Eubacterium* and *Roseburia*[14]. In fact, the short-chain fatty acids (SCFAs), including the butyrate, perform a series of beneficial functions, both local and systemic, that contribute to preserving the host's health[15]. The local actions include the maintenance of the intestinal barrier integrity, the production of mucus and an anti-inflammatory action that reduces the risk of developing colorectal cancer[16,17]. As for the systemic actions, we could list the inhibition of the activity of histone deacetylase, through which the GM regulates the immune system and the central and peripheral nervous systems[18-20].

As observed in CV diseases, an alteration of gut eubiosis is also detectable in CKD. In fact, in CKD patients there is an increase in *Enterobacteriaceae* (*Escherichia* spp., *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp.) and *Lachnospiraceae* and a decrease in *Bifidobacteriaceae* and in *Lactobacillaceae*[10,21]. Therefore, even in this pathological condition, it is evident a reduction of SCFAs-producing bacteria (responsible for the saccharolytic fermentation) and an increase in bacterial species producing uremic toxins, such as indoles, phenols and trimethylamines (responsible for the proteolytic fermentation)[22].

At this regard, it is important to develop therapeutic strategies to counteract the gut dysbiosis (namely a GM qualitative and quantitative alteration in terms of number, type and in the relative abundance of microorganisms) in CDNCDs, as it would slow down their progression and hinder the onset of their comorbidities. The adapted physical activity (APA) has aroused a considerable interest in the International Scientific Community, as it represents a new possible adjuvant treatment in the clinical management of CDNCDs, especially for its ability to positively modulate the GM.

This narrative review offers a picture of the GM role in the physiopathology of CDNCDs, in particular of CKD, and of the APA potential protective action (Figure 1). Moreover, possible exercise-based strategies are discussed according to recent scientific findings.

Search Methods Strategy

A literature search was conducted by the authors, using three online databases (PubMed, Web of Science and Scopus). Keywords used in searches included "chronic kidney disease", "CKD", "physical activity", "gut microbiota" "microbiota", "gut dysbiosis", "dysbiosis", "cardiovascular diseases", "CV diseases" and "cardiovascular risk".

Inclusion criteria consisted of studies regarding the effects of exercise on gut microbiota and CV disease in CKD patients. Moreover, some articles were excluded, if they were not in the English language, if the physical activity was not

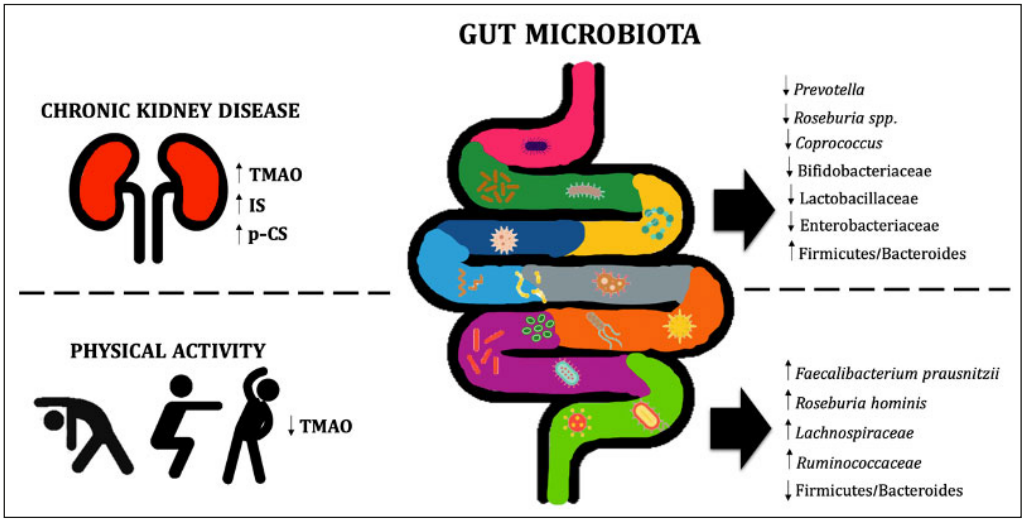

Figure 1. Impact of chronic kidney disease and physical activity on gut microbiota composition.
Abbreviations: IS, indoxyl sulfate; p-CS, p-Cresyl sulphate; TMAO, trimethylamine N-oxide.

investigated, and/or if clear results had not been reached. It also carried on a manual search of the references' list, selected through the computerized search. Once the duplicates were removed, the total search had examined 8 studies that matched the above-mentioned criteria. The flow-chart of search methods is represented in Figure 2.

Dysbiosis and Chronic Kidney Disease

As described above, the human microbiota is mainly localized in the gastrointestinal tract[23], and it plays a key role in the metabolism and absorption of nutrients. Furthermore, GM produces waste metabolites that affect organs such as the kidneys, liver and CV system[24].

The main toxic compounds able to cause a faster progression of CKD are: (i) trimethylamine N-oxide (TMAO), (ii) indoxyl sulphate (IS) and (iii) p-Cresylsulphate (p-CS). Literature data showed that these metabolites are linked to the onset of renal fibrosis, to the endothelial dysfunction and to the decline of glomerular filtration rate (GFR)[25,26]. Besides, several studies[22,27,28] demonstrated that these compounds are responsible for CV complications and for the increased morbidity and mortality in CKD patients.

Interestingly, in CKD patients, these compounds, produced by GM, can be considered uremic toxins. The CKD itself causes dysbiosis with consequent increased production of these toxins, derived by GM[22,28]. In particular, in CKD the main factors involved in GM dysbiosis are:

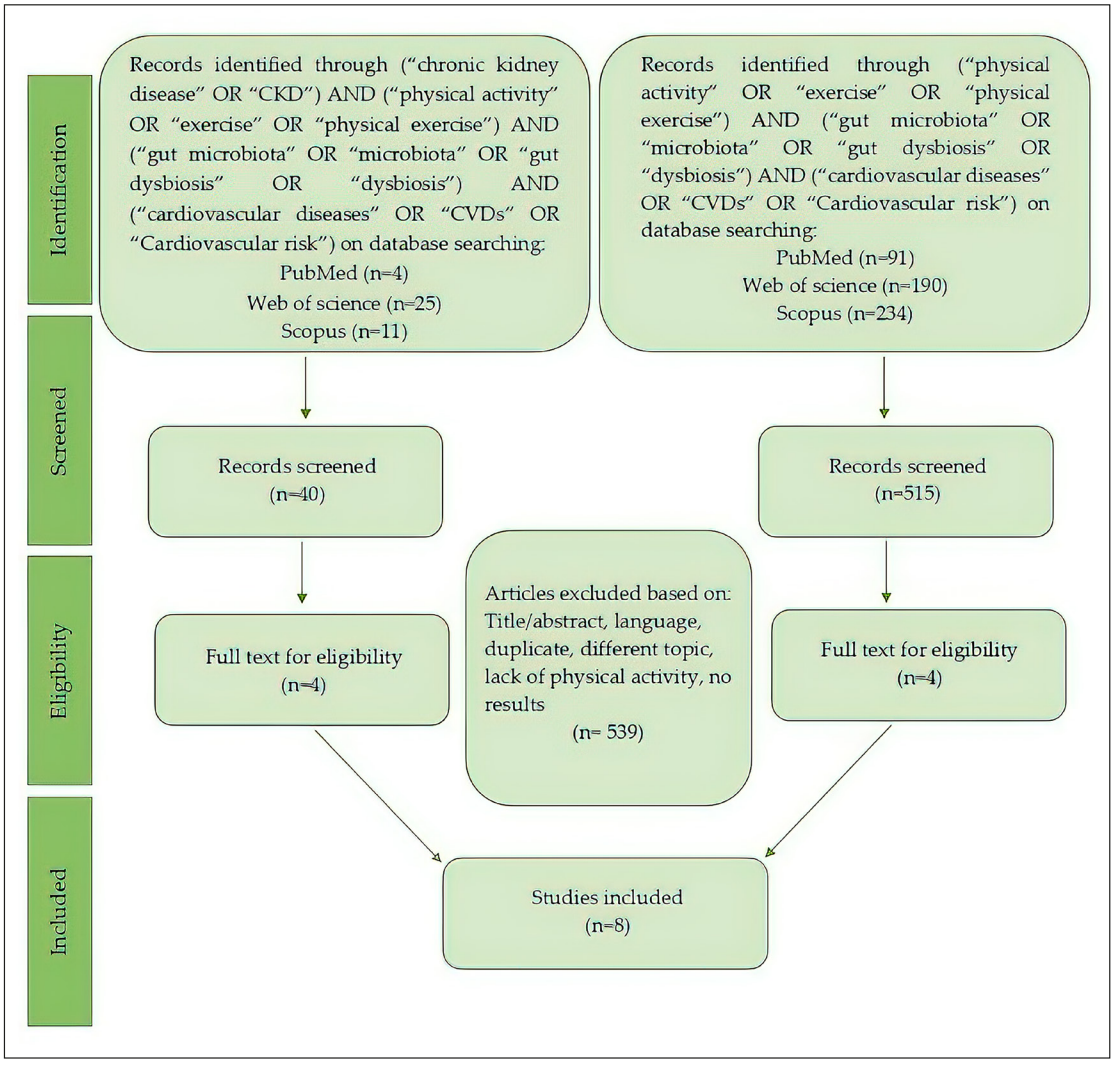

Figure 2. Search methods strategy.

a) Increased pH in the colon. This alteration induces a favorable environment for urease positive species, which can convert urea into ammonia[29]. These mechanisms determine the destruction of the intestinal barrier protective mucous layer with a consequent alteration of the tight junctions and of the intestinal permeability[29]. These processes allow the translocation of intestinal bacterial material into the bloodstream, inducing the phenomenon of endotoxemia and contributing to the development of the chronic inflammatory state, characteristic of CKD[30].
b) Polypharmacy. In CKD patients, alterations in calcium-phosphorus metabolism, in iron profile and in serum potassium concentration are observed. Consequently, this patients' population must assume for a long-time and at a high dosage, the phosphorus and potassium-binders and iron-based compounds. All these drugs seem to induce negative changes in the intestinal lumen[21,31]. In an *in vitro* study, it was shown that iron-based therapy causes a reduction in *Bifidobacteriaceae* and *Lactobacillaceae* and an increase in *Roseburia* spp. and *Prevotella*, with a consequent enhancement in the proteolytic fermentation instead of the saccharolytic one[32,33].
c) An alteration of the local inflammatory response. This phenomenon is related to the increase in *Proteobacteria*, which is capable of causing an impairment of intestinal permeability and an enhancement of the intestinal T helper 17 cells to T regulatory cell ratio. It also can favor the lipopolysaccharide translocation[34-36].

Among gut metabolites, there are also renoprotective ones, such as SCFAs. The latter exert a beneficial action by promoting the gut epithelial barrier integrity and a local anti-inflammatory response[15]. It is very important to consider that CKD causes an imbalance between saccharolytic and proteolytic fermentations, favoring the latter. As previously described, CKD patients show an increased production of gut-derived toxins and a decreased release of SCFAs. This process is responsible for the reduction of SCFAs beneficial effects, losing their tropic action on colon endothelial cells, their systemic and local anti-inflammatory action and their GM positive modulation.

An interesting study[37], known as the "Medika study", demonstrated that a reduced dietary protein intake, would seem to reduce the serum concentration of p-CS and IS, in stage III-IV CKD patients and at the same time to increase the diversity of butyrate-forming species (such as *Roseburia* spp., *Coprococcus*, etc.), after a six-month timespan. A following study[7,38] conducted by the same authors, named "Medika2 study", showed that the Mediterranean diet (MD) associated with the ketoanalogues supplementation and compared to the MD alone, appeared to be more effective in reducing the production of gut-derived uremic toxins in CKD patients.

Interestingly, Lobel et al[39] hypothesized that changes in eating habits may trigger post-translational modifications in microbial proteins, inducing negative or positive variations in the formation of uremic toxins, that could respectively speed up or slow down the CKD progression. In detail, a high-protein intake diet stimulates the GM to produce an increased amount of hydrogen sulphide, indole and IS[40].

In a CKD animal model, a diet rich in sulfur amino acids causes post-translational changes in the microbial activity of tryptophanase, by reducing the production of intestinal indoles and slowing the progression of kidney damage. Thus, a high sulphide content diet seems to be a promising tool for CKD clinical management[39].

Moreover, the assumption of extra-virgin olive oil (EVOO) with a high content of minor polar compounds (MPCs) seems to exert beneficial effects in CKD patients. In particular, an EVOO with a MPCs content above 700 ppm appears to improve purine and lipid metabolisms, body composition, inflammatory status, and oxidative stress. According to our study these effects last up to a 2-month washout[41]. In this way, we speculate that this amelioration is due to the high polyphenols content, which is able to modulate the GM composition positively[10,42,43].

Cardiovascular Complications Induced by Gut Dysbiosis Related to CKD: Role of IS, P-CS, and TMAO

In CKD patients, the concentration of p-CS and IS is a hundred times higher than that detected in healthy subjects[44,45].

As evidenced by an epidemiological study[46], CKD geriatric patients are likely to die six times more from CV causes than to suffer from end-stage renal disease (ESRD). In these patients, it is important to implement therapeutic strategies aimed at slowing down the CKD progression *vs.* ESRD, but above all, it is necessary to obtain an early diagnosis of CV comorbidities and to develop strategies aimed at counteracting them[47,48].

The IS is a gut-derived uremic toxin and it springs from the dietary amino acid tryptophan.

Once reached GM, IS is metabolized into indole by specific enzymes, named tryptophanase. Indole crosses the gut barrier and spreads into the bloodstream and subsequently, it is converted into IS in the liver. In subjects with normal renal function, IS is excreted in the urine. On the contrary, in the presence of CKD, IS plasma levels increase[49,50]. IS high levels seem to represent a new risk factor for CV diseases since the IS accumulation induces vascular calcifications, arterial stiffness and cardiac fibrosis[51]. Moreover, IS may be involved in the development of peripheral vascular disease and the thrombotic events of the hemodialysis vascular access[52].

p-CS is another gut-derived uremic toxin that appears to represent an additional CV risk factor, as it exerts a cardiotoxic action[53]. These data were supported by a study conducted on an animal model in which, in 5/6 nephrectomized rats, p-CS was able to induce oxidative stress through an increased production of reactive oxygen species (ROS), by activating NADPH-oxidase and caspase-3. As a matter of fact, this mechanism causes cardiomyocytes apoptosis[53].

TMAO is another gut-derived toxin, involved in increasing CV. TMAO plasma levels and those of its metabolic precursors (like choline, L-carnitine and betaine) appear to be directly associated with CV events, such as myocardial infarction, stroke and death[54,55].

In animals, the TMAO biological functions are to promote bacterial growth through the acceptance of an electron, during the aerobic respiration process, and to preserve the protein structures. Up to now, it has not been detected its physiological role in humans[56,57].

As well as for other mammals, in humans the TMAO production occurs in two steps. Firstly, GM metabolizes the substrates containing TMAO, assumed through foods such as red meat, fish, and eggs. Secondly, gaseous trimethylamine (TMA) reaches the bloodstream and it is oxidized by the liver enzyme, flavin monooxygenase isoform 3, to form TMAO[58].

The main mechanisms by which TMAO contributes to increase CV risk are three: i) alteration of lipid metabolism; ii) platelet dysfunction; iii) formation of foam cells[59]. In fact, literature data demonstrated that TMAO increased levels are associated with a 1.7-fold enhanced risk for major adverse CV events compared to subjects with low TMAO levels[54]. Interestingly, these associations did not differ in a statistical way, when adjusted for the past medical history of CV diseases, diabetes mellitus, obesity and CKD[54], confirming the possible role of TMAO as a CV risk potential independent predictor[54].

TMAO has been reported[60] to exert an atherogenic action, as it impairs cholesterol and bile acids metabolism, and it activates inflammatory pathways.

Role of Physical Activity on Gut Microbiota Changes

As previously mentioned, in addition to non-modifiable host factors (like gender, age, ethnicity, etc.), the gut bacterial population seems to be modulated by extrinsic host factors such as lifestyle behaviors, APA and dietary habits[61,62]. Recent studies[64,65] highlighting the relationship between GM and exercise, indicate that the latter may play a positive role in modifying the quantity and quality of GM composition. Most of the studies were conducted on animal models. Choi et al[63] showed changes in the GM composition in mice that performed physical activity *vs.* sedentary mice. The exercise group revealed differences in 2,510 taxa of bacteria compared to the sedentary group: mice that performed physical activity presented more abundance of the *Lactobacillales* order and a decrease of the *Tenericutes* phylum than sedentary mice. Similar results were reported by Queipo-Ortuño et al[64], underlining that exercised rats showed an increase in *Lactobacillus* and *Blautia coccoides/Eubacterium rectale*. Moreover, a study[65] carried out on different strains of rats demonstrated an increase in bacterial diversity in the exercised group and, more specifically, an increase in the genus *Lactobacillus* in obese rats receiving physical activity. Currently, it is not fully understood how exercise may induce changes in GM. However, the observed changes seem to involve several factors and pathways, as reported below.

a) Bile acids: the exercise may induce modifications in the bile acids profile, causing alterations in GM. Studies reported[66,67] an inverse relationship between the amount of fecal bile acids and physical activity.

b) SCFAs: the exercise seems to affect the fecal SCFAs profile, supporting the relationship between muscle mass and GM. Experiments in animal models show that the running increases fecal butyrate levels and this change is associated with a variation in butyrate-producer bacteria groups[68].

c) Myokines: patients affected by inflammation-related diseases, such as inflammatory bowel diseases, CV diseases and diabetes mellitus, indicate GM dysbiosis[69]. The practice of a regular physical activity induces the release of myokines (like cytokines and other peptides) from muscle fibers, which, in turn, stimulate anti-inflammatory pathways[70]. However, the relation between myokines released from the muscle and GM is not clear yet.

d) Weight loss: obese and non-obese subjects differ in the GM composition[71,72]. The exercise, reducing the body weight and modulating the body composition, can induce changes in the GM. This relation needs further research.

e) Gut transit time: a moderate exercise leads to a reduction in the bowel transit time[73], which seems to affect the GM composition. Constipated obese children show a decrease in phylum *Bacteroidetes* and genus *Prevotella* in their GM when compared with the GM of normal intestinal transit time obese children[74]. Moreover, exercise performed at high intensity and for a long period (i.e., long-distance running and triathlon) may induce diarrhea and gastrointestinal bleeding[75]. These alterations in gut permeability produce a phenomenon of ischemia and reperfusion that can influence the GM composition.

f) Stress and hypothalamic-pituitary-adrenal (HPA) axis: certain populations of bacteria are modulated by the activation of the HPA axis[76]. These bacteria can produce hormones, which modify the host behaviour[77], improving the answer to the stress and modifying the GM composition. Different types of physical activity can produce physical stress and homeostasis disruption, especially when the intensity is more than 60% of the maximum volume of oxygen (VO_{2max}) or when the duration of exercise exceeds 90 minutes, inducing HPA axis activation[78]. In addition to physical stress, athletes in pre-competition periods suffer from high psychological stress[79], which can also induce HPA axis activation. According to this evidence, the exercise intensity and duration can modify the GM profile through the release of hormones.

Further studies on the mechanisms linking exercise and GM are needed to fully understand the specific impact of exercise on GM health. However, it is well known that an active lifestyle, involving moderate exercise, leads to positive effects on GM diversity and composition, contributing to host health[80]. It is still necessary to investigate about the relationship between different characteristics of the exercises, such as frequency, intensity, time and type (FITT parameters) and which might be the most appropriate exercise in the different pathological conditions (CV diseases, CKD, diabetes mellitus, etc.).

In light of this evidence, it seems that APA could represent a new tool in the clinical management of CDNCDs, especially for its ability to modulate the GM positively.

Physical Activity May Positively Modulate Gut Microbiota, Reducing Cardiovascular Risk Factors in a High-Risk Population

Nowadays, the effect of physical activity in decreasing CV risk factors is well recognized[81]. In the last decades, researchers focused their attention on the impact of physical activity on GM, trying to understand its potential involvement in health promotion and its role in CV diseases[82].

CV, metabolic and kidney diseases are characterized by a chronic low-grade inflammation, which is recognized as one of the main physio-pathological mechanisms that alters the microbiota composition[83]. At this regard, physical activity represents a strong anti-inflammatory non-pharmacological strategy in the management of patients with cardiometabolic diseases[84,85]. Physical activity, influencing the quantity and the quality of microbial communities, seems to activate pro-inflammatory and/or anti-inflammatory pathways, which regulate the low-grade inflammation[86,87]. On the other hand, sedentary lifestyle and physical inactivity are the main modifiable risk factors for CV diseases and they influence in different ways the microbial composition. Recently, Bressa et al[88] studied the differences in GM profile between active and sedentary women. The authors observed that women, that perform at least the minimum levels of physical activity recommended by the World Health Organization (3 hours/week), showed an increased concentration of butyrate producers' species such as *Faecalibacterium prausnitzii* and *Roseburia hominis*. In fact, butyrate is produced from the bacterial fermentation of dietary fibers and its low levels are associated with an increased risk of developing CV diseases[14]. In subjects at high atherosclerotic risk, a six-day lifestyle change (nutritional intervention, stress management education, daily exercise, and yoga classes) is associated with an enhanced production of SCFAs, especially of butyrate[89]. In par-

ticular, at the end of the intervention, the increase of *Lachnospiraceae*, *Ruminococcaceae*, and *Faecalibacterium prausnitzii* species were indirectly related to body mass index (BMI), blood pressure, total cholesterol, high-sensitivity C-reactive protein, glucose and TMAO levels. These results suggest that a lifestyle correction intervention, characterized by a program of physical activity, might be a promising non-pharmacological preventive strategy to improve CV health[82].

Several studies[90,91] based on enterotype stratification (enterotype 1, 2 and 3) analyzed the association of human GM composition and cardiometabolic risk factors. Enterotype 3 seems to be strongly related to the development of CV diseases. In fact, it increases the morbidity and mortality of subjects with pre-existent CV high-risk, such as hemodialysis patients[92]. Besides, enterotype 3 is characterized by an over-representation of *Firmicutes*, mainly *Ruminococcus*, and *Ruminococcaceae*, and a less abundance of *Bacteroides*, *Prevotella*, and *Xylanibacter*. On the contrary, the latter is more abundant in enterotypes 1 and 2[92,93].

Physical activity seems to induce microbial variance, affecting *Firmicutes/Bacteroidetes* ratio[94]. Studies performed[95,96] on an animal model showed that an early life exercise increases *Bacteroides* and decreases *Firmicutes*, changing the GM composition[95]. Even the controlled dietary intake, combined with regular physical activity levels, seems to lead to a reduction in several *Firmicutes* species[96].

In overweight and obese subjects, affected by metabolic syndrome, 1-year of energy-restricted MD and increased physical activity levels, reduced *Butyriciccocus, Haemophylus*, *Ruminiclostridium* 5 and *Eubacterium hallii*[96].

A higher *Firmicutes/Bacteroidetes* ratio appears to be significantly correlated with VO_{2max}[97], which is a cardiorespiratory fitness predictor with a protective role on the CV diseases onset[98]. These findings suggest that an adequate caloric intake combined with physical activity may positively influence CV risk through the GM modulation. Furthermore, the *Firmicutes/Bacteroidetes* ratio seems to be inversely related to the amount of exercise performed[99]. This ratio suggests the importance of intensity, volume, duration and frequency of physical exercise, because the effect on GM seems to be transient and reversible when the training is concluded[100]. Moreover, Allen et al[100] evidenced that aerobic exercise can modulate GM and the production of SCFAs in both lean and obese subjects. Therefore, this phenomenon proves that regular exercise is mandatory to achieve a healthy lifestyle, although the relationship between different types of physical activity (like endurance or resistance) and eubiosis has not been investigated enough yet.

Physical activity intensity is a potential mechanism able to decrease the risk of cardiometabolic diseases, influencing the levels of bioactive metabolites that exert cardioprotective actions. It was widely demonstrated the protective and preventive role of daily moderate to vigorous physical activity (MVPA) on cardiometabolic health, affecting different metabolic pathways involved in the systemic inflammation and in the imbalance of glucose and lipid metabolisms[101-103].

Argyridou et al[104] studied the association between MVPA levels and TMAO in subjects at risk of type 2 diabetes mellitus. In this study, 30 minutes *per* day of MVPA were associated with lower TMAO levels. On the contrary, a sedentary lifestyle or light physical activity were not related to the changes in TMAO levels, suggesting that the intensity of movement may be relevant. These results indicate that physical activity, characterized by specific volume and intensity, can regulate cardiometabolic health through the TMAO levels modulation. Moreover, lifestyle interventions, including the exercise, may affect TMAO.

Erickson et al[105] randomly assigned sixteen obese adults to a 12-week lifestyle correction intervention. It consisted of a hypocaloric or normocaloric diet, combined with 5 days/week of aerobic exercise, performed for 50-60 minutes, at 80-85% HRmax. The authors concluded that the combination of a hypocaloric diet with training appears to be effective in reducing the TMAO levels in obese adults. Differently, the effect of training, combined with a normocaloric diet, was less effective on TMAO levels reduction. Thus, the TMAO production may be more responsive to the combination between physical activity and hypocaloric diet than physical activity alone, emphasizing the importance of an overall approach, combining a well-tailored exercise with a personalized diet.

According to Randrianarisoa et al[106], the TMAO average baseline levels seem to predict a positive response to a lifestyle correction intervention. The authors studied the effect of a low-fat diet combined with moderate exercise training (3 hours *per* week) in subjects at risk of type 2 diabetes mellitus. After a 9-month intervention, the authors observed that TMAO levels did not change, while most cardiovascular risk parameters improved[106]. However, they suggested that TMAO level is directly associated with carotid intima-media thickness (CIMT), independent-

ly from other cardiovascular biomarkers. CKD and type 2 diabetes mellitus patients have higher circulating levels of TMAO produced by gut bacteria and consequently an elevated risk for CV diseases[107]. These studies[106,107] highlight the potential new mechanisms that may prevent and protect CKD patients from CV complications.

To our knowledge, only De Brito et al[108] evaluated the effects of different exercise programs on gut-derived uremic toxins levels in hemodialysis patients. These authors analyzed IS, p-CS, indole acetic acid (IAA) and TMAO. CKD patients were randomized into an intradialytic aerobic exercise group, in an intradialytic resistance exercise group and in a control group. Aerobic exercise was performed on a bike during the first two hours of the hemodialysis session, three times/week for three months (4-5 Borg scale intensity). The resistance group performed exercises with elastic bands during the first two hours of the hemodialysis session, three times/week, for six months. The control group received the standard care. The results showed that physical activity did not impact on gut-derived uremic toxins levels[108]. However, the

Table I. Effects of physical activity on gut microbiota and cardiovascular risk.

Author	Year	Study Population	Intervention	Outcome
Bressa et al[88]	2017	40 premenopausal women	ActiSleep V.3.4.2 accelerometer (ACT): 7 d·wk (n=19) SED: (n=21)	ACT increases *Faecalibacterium prausnitzii, Roseburia hominis*
Ahrens et al[89]	2021	73 patients with ASCHD risk	LSC: 1 wk, NE 15 h·wk, SE 2 h·wk, FE 5h ·wk, SA 3 h·wk	LSC decreases blood pressure, total cholesterol and triglycerides, enhances production of SCFAs and butyrate
Muralidharan et al[96]	2021	400 overweight and obese patients with MS	IG: FE and Energy reduced MedDiet (n=200) CG: non-energy-restricted MedDiet (n=200)	In IG reduction of several Firmicutes species: *Lachnospiraceae* (a SCFAs producers)
Allen et al[100]	2018	32 lean and obese participants	MVAT: 3d·6wk·30-60 min at 60-75% HR	MVAT modulates gut microbiota and SCFAs
Argyridou et al[104]	2020	483 participants at high risk of Type 2 Diabetes	Accelerometer (ActiGraph GT3X, Pensacola, Florida, USA) 7 d·wk	30 m·day of MVPA was associated with lower TMAO levels; Sedentary o LPA were not associated with TMAO changes
Erickson et al[105]	2019	16 Obese adults	HYPO: 12 weeks of exercise, 5 days·week, 80-85% HRmax + hypocaloric (-500 kcal) diet (n=7) EU: same exercise + normocaloric diet (n=9)	HYPO decreased and EU increased the percentage change in TMAO; Absolute TMAO levels were not modified
Randrianarisoa et al[106]	2016	220 participants at high risk of Type 2 Diabetes	LSC: 9 mon NE 10 sessions + FE 3h·wk Moderate AT	Higher TMAO levels predicted increased carotid intima-media thickness (CIMT)
De Brito et al[108]	2022	46 CKD patients on HD	Exp1[AT: 3mon 3d·w (n=11) CG: no exercise (n=9)] Exp2 [RT: 6mon 3 d·w (n=14) CG: no exercise (n=12)]	No impact on gut-derived uremic toxins levels

ACT, active; SED, Sedentary; MPA, Moderate Physical Activity; LPA, Light Physical Activity; MVPA, Moderate to Vigorous Physical Activity; ASCHD, High Atherosclerotic Cardiovascular Disease; MS, Metabolic Syndrome; LSC, Life Style Change; NE, Nutritional Education; SE, Stress reduction Education; CE, Cooking Education; FE, Fitness; SA, Sport Activity; AT, Aerobic Training; CKD, Chronic Kidney Disease; d, day; HR, Heart Rate; mon, month; CG, Control Group wk, week; Exp, Experiment.

study did not consider the analysis of the GM composition, highlighting the need to increase knowledge about the efficacy of physical activity in hemodialysis patients.

To date, an appropriate and personalized lifestyle intervention, characterized by a program of physical activity associated with a tailored diet, seems to be an effective non-pharmacological approach to maintain the GM eubiosis. Physical activity appears to be a promising tool in the management of CKD, reducing the CV risk. Future studies, regarding the impact of physical activity on the GM composition in CKD patients, are necessary to better understand how physical exercise can induce the GM modulation (Table I).

Conclusions

In recent literature it was confirmed the bidirectional relationship between the GM and the kidney function.

CV diseases seem to have a negative impact, through GM alteration, on the prognosis and the survival of CKD patients. Consequently, it is necessary to develop strategies aimed at reducing the CV risk in patients affected by CDNCDs.

Because of the limited alternative strategies able to improve the GM composition in CDNCDs, in particular in CKD patients, it seems to be of considerable interest the identification of non-pharmacological interventions capable of inducing eubiosis. In fact, the dysbiosis, characterized by an increased production of compounds and derivatives of proteolytic fermentation, is directly related to an enhanced CV risk.

To our knowledge, the literature reviewed herein indicates that aerobic exercise might be a promising adjuvant strategy to induce beneficial changes in the GM composition of CKD patients, reducing at the same time the CV risk. Future studies are required to analyze the different impact of FIIT parameters on the GM modulation in CDNCDs patients, as well as to elucidate the molecular mechanisms underlying these beneficial effects. These findings could support the importance to introduce physical activity programs into guidelines for the clinical management, not only for CKD patients, but also for those with other CDNCDs.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

Availability of Data and Materials
Not applicable.

Conflicts of Interests
The authors declare no conflict of interests.

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Authors' Contributions
AN, ET, NDD, AP, CC, conceptualization; GM, EG, MDL, AM, GV, DCDM, MT, original draft preparation; AN, AP supervision; GM, AM, visualization.

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