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TOPICAL REVIEW

Exercise-induced changes to the human gut microbiota and implications for colorectal cancer: a narrative review

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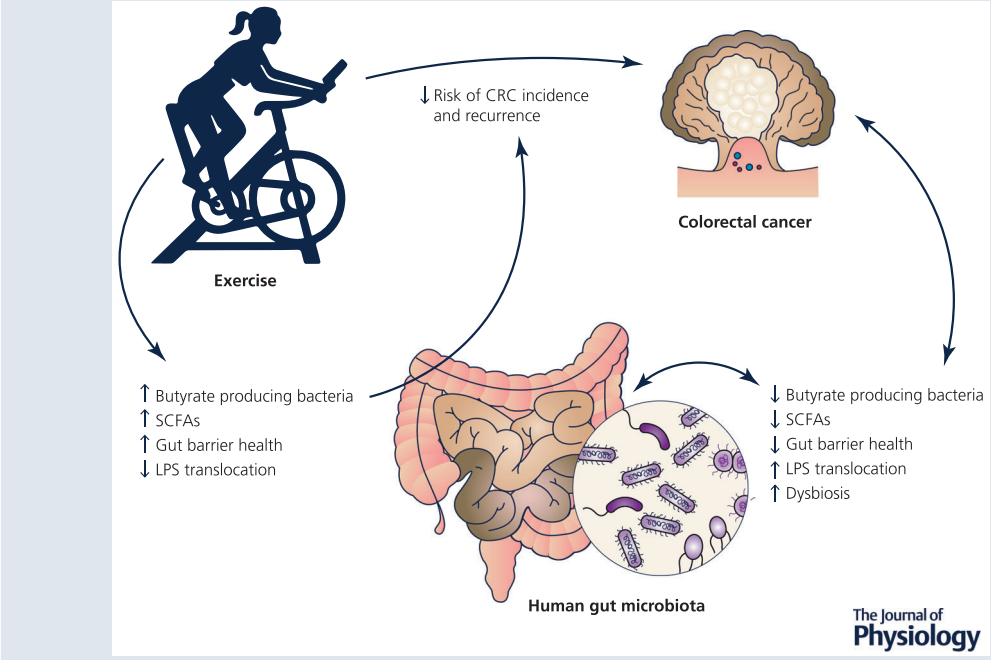

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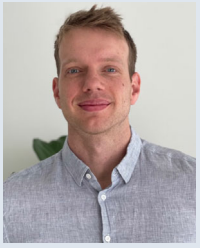


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Abstract Physical activity is associated with reduced risks of colorectal cancer (CRC) incidence, recurrence and mortality. While these findings are consistent, the mechanism/s underlying this association remain unclear. Growing evidence supports the many ways in which differing characteristics of the gut microbiota can be tumourigenic or protective against CRC. CRC is characterised by significant dysbiosis including reduced short chain fatty acid-producing bacteria. Recent findings suggest that exercise can modify the gut microbiota, and these changes are inverse to the changes seen with CRC; however, this exercise-microbiota interaction is currently understudied in CRC. This review summarises parallel areas of research that are rapidly developing: The exercise–gut microbiota research and cancer–gut microbiota research and highlights the salient similarities. Preliminary evidence suggests that these areas are linked, with exercise mediating changes that promote the antitumorigenic characteristics of the gut microbiota. Future mechanistic and population-specific studies are warranted to confirm the physiological mechanism/s by which exercise changes the gut microbiota, and the influence of the exercise–gut interaction on cancer specific outcomes in CRC.

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Abstract figure legend The exercise–gut microbiota interaction appears to produce changes that may protect against colorectal cancer, explaining, at least in part, the inverse relationship between exercise and colorectal cancer.

Background

Exercise is a potent tool for reducing the risks and severity of chronic diseases, including colorectal cancer (CRC) (Cormie et al., 2017). Indeed, exercise has been shown to improve quality of life, cancer-specific mortality and all-cause mortality in those with and surviving CRC (Balhareth et al., 2019; Cormie et al., 2017; Mishra et al., 2012). CRC is the third most diagnosed cancer worldwide and the second leading cause of cancer mortality (Sung et al., 2021). Despite the high rates of disease diagnosis, continual improvements in early disease identification and anticancer therapies means that the number CRC survivors continues to grow (Australian Institute of Health & Welfare, 2021). However, survival is accompanied by high risks of cancer recurrence and cancer-related mortality, as well as long-term debilitating consequences of treatment-related side effects that increase the risk of developing comorbidities, reduce mental health and affect quality of life (El-Shami et al., 2015; Han et al., 2020; Lim et al., 2021). Exercise has consistently been shown to improve outcomes for those who have been diagnosed and treated for CRC (Singh et al., 2020). However, the biological mechanism/s responsible for these improvements are not clear.

A possible mechanism to explain the inverse relationship between exercise and CRC involves the gut microbiota. Gut health has been associated with the risk of colon cancer (Louis et al., 2014; Song & Chan, 2019), and emerging evidence suggests that exercise-mediated changes to the gut microbiota may also influence risk of the disease (Allen, Mailing, Niemiro et al., 2018; Cook et al., 2016; Mailing et al., 2019; Zhao et al., 2018). The aim of this review is to explore evidence of the interplay between exercise, the gut microbiota and the risk of CRC.

Considerations for microbiota interpretation in human studies

An important consideration when interpreting the current body of literature exploring exercise-induced changes in microbiota and microbiome in humans is methodological heterogeneity (Mailing et al., 2019). In this review, we will refer to the gut microbiota as the collection of microbes within the gut (Bacteria, Archaea, Eukarya, and their viruses) and the microbiome as the collective community of microbes, its gene expression, and activity. Generally, analytical techniques fall into two categories: 16S rRNA gene amplicon (also termed rDNA) and shotgun metagenomic sequencing. Practically, these two approaches enable the determination of the bacterial taxonomic composition and help interpret their function (i.e. interaction with their environment and the host). Shotgun metagenomic sequencing enables direct observation of both the abundance of the different species present in the gut microbiota and of the genes present in these species enabling an analysis of possible functions. Combined with mRNA, protein, and metabolite analysis, this can give a good indication of what the bacteria in the gut are doing and how they interact with the host

(Mailing et al., 2019). Most studies in this area have utilised stool samples as a representation of the gut microbiota and historically, 16S rRNA gene amplicon sequencing has been used to assess the taxonomic profile of the gut microbiota (Dziewiecka et al., 2022). Based on these amplicon profiles, bioinformatic workflows such as phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt2) (Douglas et al., 2020) can support inference of the functionalities inherent to gut microbiota. Alternatively, fecal metabolite measures can provide some understanding of the microbiome; however, factors such as metabolite production rates, their translocation and cross-feeding may not be accounted for with these measurements (Goyal et al., 2021; Spiljar et al., 2017). When considering those studies that have used higher sensitivity analyses of microbiota composition and metabolites, the evidence suggests that the changes in microbial abundance observed with exercise training significantly change the function of the gut microbiome (Barton et al., 2018; Keohane et al., 2019; O'Donovan et al., 2020; Petersen et al., 2017). These same changes may also have occurred in earlier studies that used less sensitive analysis such as 16S rRNA gene amplicon sequencing and although function of the identified bacteria can be estimated using less sensitive analysis, gene expression cannot be assessed. Previously, an important benefit to lower sensitivity assessment has been a lower cost per sample and ease of analysis – however, these are becoming less of an issue, at least with samples containing large amounts of microbial DNA (e.g. stool).

A second key consideration, proposed recently by Shanahan et al. (2021), relates to the complexity of defining a 'healthy' microbiome, with implications for how microbiota research may be discussed in a clinical setting (Shanahan et al., 2021). A 'healthy microbiome' is most likely best defined using functional rather than taxonomic descriptors. For example, Lloyd-Price et al. (2016) suggested that a microbiome must be "resistant, resilient, and stable" to perturbation and thereby, the functional 'housekeeping' aspects of the gut microbiota are maintained. However, defining a 'healthy' microbiome is no small challenge, given the significant inter- and intra-variability that exists for the gut microbiota, as well as the functional diversity and redundancy inherent to different microbes. Furthermore, factors such as age, genetics, diet, lifestyle choices and/or medications can all coalesce and manifest to change the functional attributes of the gut microbiota (e.g. Song, Chan, & Sun, 2020). Indeed, Shanahan et al. (2021) question the use of 'healthy' to describe the gut microbiome without sufficient contextual depth, and going forward, greater efforts need to be made in terms of standardising objective measures of subjects health status as part of any clinical or nutritional studies.

In summary, marker gene (e.g. 16S rRNA) assessments of the gut microbiota have and still enable the recording of crucial evidence across many populations (and sites within the gastrointestinal tract) and can show how exercise interventions potentially influence the microbiome (Cronin et al., 2016; Mailing et al., 2019). However, recent and emerging advances in 'multi-omics' methods will offer new opportunities to better establish the functional aspects underlying the findings from previous and future research. Acknowledging this, our review aims to highlight the most consistent findings in the current literature and discuss these in the context of changes with exercise and cancer risk mitigation.

Exercise and the gut microbiome

Murine models of exercise have shown consistent changes in the gut microbiome that are often associated with improved health and longevity (Mailing et al., 2019). The controlled nature of these studies has enabled evaluation of the mechanistic interactions between exercise and the gut microbiota as well as highlighting the potential power of the gut microbiome to be a mediator of health outcomes in response to exercise. For example, one key study highlighted that exercising individuals presented with significantly different microbiota profiles than sedentary individuals (Allen, Mailing, Cohrs et al., 2018). Upon transplantation of these microbiota to germ-free mice, mice receiving a transplant from exercising individuals experienced positive changes in body composition compared to the sedentary transplant group (Allen, Mailing, Cohrs et al., 2018). Acknowledging the limitations of transplant viability and donor acceptance, as well as the translatability of murine models to humans, this study provides a conceptual framework showing how exercise can influence the gut microbiota, which in turn promotes physiological adaptations conducive to positive health outcomes.

Crucial conceptual works have explored the mechanisms underpinning the influence of exercise on the gut microbiome (Cronin et al., 2016; O'Sullivan et al., 2015). Reduced splanchnic flow, altered enteric nervous system innervation, interaction with the vagal nerve innervations and their systemic influences, as well as cytokine and myokine interactions in response to exercise have been suggested as mechanisms altering the gut microbiota profile and improving overall health and wellbeing – further evidence is required (Cronin et al., 2016). Mailing et al. (2019) concluded that changes to the gut microbiome with exercise may contribute to reductions in conditions such as metabolic syndrome, cognitive decline, as well as depression, and anxiety. In order to leverage the gut microbiome through exercise to improve and optimise health, further research is required. Research illuminating the specific mechanisms

linking exercise and the gut microbiome will be especially relevant to allow understanding of how they may be utilised clinically.

Foundational work of exercise–gut interactions in humans discovered that athletes (professional rugby players) have greater microbiome diversity, greater abundance of metabolic pathways and more expression of genes within their gut microbiome for carbohydrate biosynthesis, amino acid biosynthesis and energy metabolism than healthy male controls (Clarke et al., 2014). Important to note, the control group in this study still conducted significant physical exercise based on a self-reported questionnaire and creatine kinase (CK), with average yearly vigorous exercise reported as 7.21 h per week for low BMI controls and 3.85 h per week for high BMI controls. Using these metrics does introduce limitations to accurately quantifying exercise, and future research would benefit from improved methodology. Acknowledging this, the study found significant associations with exercise and microbial changes, between groups despite both groups conducting some exercise, suggesting a possible dose response (Clarke et al., 2014). Microbial short chain fatty acid (SCFA) production was also greater in the athletes compared to healthy males with a body mass index (BMI) <25 kg/m^2, due to a higher abundance of SCFA-producing bacteria (Clarke et al., 2014). Subsequent studies confirmed greater abundance of SCFA producers and particularly butyrate with exercise in a variety of populations (Allen, Mailing, Niemiro et al., 2018; Barton et al., 2018). Regression modelling by Estaki et al. (2016) found that cardiorespiratory fitness explained 20% of the variation in gut diversity. The authors suggested the functional attributes of the gut microbiota community, rather than taxonomic profile, paralleled these differences in cardiorespiratory fitness. Collectively, these studies suggest that a history of exercise is associated with greater gut microbiota diversity and higher SCFA production.

Growing evidence from observational and controlled trials suggest that the gut microbiota can change in response to an exercise intervention. In one investigation, performing a half-marathon was found to elicit significant acute changes in the abundance of specific gut bacteria (Zhao et al., 2018). In another study, completing an ultramarathon increased the relative abundance of potentially infectious bacteria while the relative abundances of bacteria associated with markers of health decreased (Grosicki et al., 2019). The findings from these two studies, albeit with a few subjects, does suggest that exercise can evoke a rapid alteration to the gut microbiota.

Most studies that have reported changes to the gut microbiome in response to exercise training have been conducted in active or trained participants (Clarke et al., 2014; Colbey et al., 2017; O'Donovan et al., 2020). A study of sedentary participants reported that following 6 weeks of exercise training (1 h continuous exercise at 60–75% heart rate reserve, three times per week), the greatest positive change in microbial diversity, abundance and SCFA production occurred in lean individuals (BMI <25 kg/m^2) compared to those with a high BMI (≥ 30 kg/m^2) (Allen, Mailing, Niemiro et al., 2018). Significant correlations between exercise and the abundance of butyrate-producing taxa were observed – but only in lean individuals (Allen, Mailing, Niemiro et al., 2018): lean mass was highly correlated with the abundance of these bacteria ($r = 0.70$, $P < 0.01$), fecal butyrate concentrations ($r = 0.87$, $P < 0.01$) and gene expression of butyrate production enzymes (BCoAT; $P < 0.05$). Moreover, percentage body fat was negatively correlated with butyrate-producing bacteria ($r = -0.57$, $P < 0.05$) and butyrate concentrations ($r = -0.5$, $P < 0.05$) (Allen, Mailing, Niemiro et al., 2018). Further research is required to determine whether this trend is consistent or whether augmentation of exercise prescription (e.g. higher intensity) may overcome the influence of body composition.

Though the mechanisms responsible for the changes in the gut microbiota with exercise are not well understood, several have been proposed (Mailing et al., 2019). Exercise may alter the gene expression of intraepithelial lymphocytes residing within the gastrointestinal tract, promoting the release of anti-inflammatory cytokines, and enhancing microbial homeostasis (Hoffman-Goetz et al., 2009; Ismail et al., 2011; Packer & Hoffman-Goetz, 2012). Other potential mechanisms include altered integrity of the gut mucus layer, increased core temperature, reduced intestinal blood flow during exercise and subsequent reperfusion during rest, improved gut motility and activity of the enteric nervous system, which may impact intestinal pH, mucosal secretion, and availability of nutrients for the microbiome following exercise. In addition, a wide range of literature has shown that the exercise-induced release of myokines, metabolites and neuroendocrine hormones from skeletal muscle may interact with the gut (Dainese et al., 2004; Egan & Zierath, 2013; Fehrenbach et al., 2000; Freeman et al., 2006; Kakiyama et al., 2013; Karol et al., 2006; Lira et al., 2010; Meissner et al., 2011; Otte et al., 2001; Song et al., 2012; Vital et al., 2014; Wijck et al., 2011). Further research is required to illuminate the mechanisms that can be practically leveraged to modify the gut microbiota, as well as how these mechanisms may interact with health. Indeed, many of these mechanisms are likely to have crossover with disease risk or protection in those with cancer.

Exercise, the human gut microbiome and cancer risk

Changes in the microbial community in response to exercise training in healthy individuals commonly involve changes in the relative abundances of *Akkermansia*

(Barton et al., 2018; Bressa et al., 2017; Clarke et al., 2014; Kern et al., 2020; Munukka et al., 2018; Petersen et al., 2017), *Ruminococcus* (Bycura et al., 2021; Kern et al., 2020; Petersen et al., 2017; Zhao et al., 2018), *Veillonella* (Grosicki et al., 2019; Keohane et al., 2019; Motiani et al., 2020; Scheiman et al., 2019), and *Lachnospira* (Allen, Mailing, Niemiro et al., 2018; Bycura et al., 2021; Langsetmo et al., 2019; Motiani et al., 2020; Whisner et al., 2018). There is also evidence that the relative abundances of *Prevotella* (Clarke et al., 2014; Keohane et al., 2019; Langsetmo et al., 2019; Petersen et al., 2017), *Faecalibacterium* (Allen, Mailing, Niemiro et al., 2018; Bressa et al., 2017; Grosicki et al., 2019; Langsetmo et al., 2019; Motiani et al., 2020; Yu & Wang, 2018), *Roseburia* (Bressa et al., 2017; Estaki et al., 2016; Keohane et al., 2019; Paulsen et al., 2017) and other non-specific butyrate producers (Allen, Mailing, Niemiro et al., 2018; Barton et al., 2018; Estaki et al., 2016) can also change with exercise. Of note, the abundance of the species *Akkermansia muciniphila* is inversely related to a key biomarker of inflammation (C-reactive protein) and may be implicated in reduced CRC risk (Al Bander et al., 2020). A common theme of all these changes in the gut microbiota coincident with exercise relates to gut homeostasis, immune function and systemic inflammation, the latter two of which have long been associated with promoting the formation and development of CRC and other cancers (Al Bander et al., 2020; Long et al., 2017; Terzić et al., 2010). The gut microbiome has also been shown to influence CRC risk via multiple routes including altered metabolite production, DNA damage, derangements in cellular processes and immune responses that contribute to microenvironmental conditions that can initiate and propagate CRC (Louis et al., 2014; Sears & Garrett, 2014). Previous reviews have described these interactions in detail (Al Bander et al., 2020; Long et al., 2017; Louis et al., 2014; Sears & Garrett, 2014; Sepich-Poore et al., 2021), so here we summarise the findings related to immunity, inflammation and microbially driven cancer, as well as mechanisms shown to be protective against cancer. Importantly this summary is further refined to discuss mechanisms that may be involved in the exercise–gut interaction and its conceptual relationship to colorectal cancer.

The gut microbiome has been identified as a key regulator of innate and adaptive immunity both locally and peripherally. For example, gut dysbiosis is typified by an enrichment of opportunistic pathogenic bacteria that impair immune function and lead to a heightened inflammatory state both local and distal to the gut (Spiljar et al., 2017). A brief summary of the mechanisms and actions linking CRC formation and proliferation to the gut are shown in Table 1; more detailed information, particularly relating to how the microbiome influences immunoglobulin A production, T cell, TH17, and dendritic cell regulation and immune 'tone', as well as influencing cytokine and interferon activity both local and distal to the gut, can be found elsewhere (Gopalakrishnan et al., 2018).

Exercise has been shown to influence the gut environment, most commonly altering the habitability of microbes as addressed previously in this review. In contrast to dysbiosis, changes that occur with exercise generally upregulate the abundance of bacteria that are routinely associated with improved health, including improvements in immune function and inflammatory profiles. Exercise-mediated positive changes in gut microbiome diversity and increased abundance of the aforementioned microbes appear to prevent dysbiosis and may explain, at least in part, the reduced the risk of cancer formation and progression with exercise. Furthermore, the specific changes seen in the microbiome with exercise cross over with many mechanisms suggested to be protective against CRC such as upregulation of butyrate producing bacteria.

The 'commensal' gut microbiota have long been recognised to confer protective, structural and nutritional inputs promoting gut homeostasis (Grenham et al., 2011). By extension, these inputs are likely to have protective and/or mitigating effects that reduce CRC incidence and appear to be promoted with exercise. While a detailed overview of these fields of research is beyond the scope of this review, there are three general ways in which the gut microbiota can contribute to reduced CRC risk. Central to each of these is the maintenance of higher gut microbial diversity (Ahn et al., 2013; Machiels et al., 2014).

First, a more diverse commensal microbiota promotes gut barrier integrity (Schroeder & Bäckhed, 2016; Spiljar et al., 2017), which minimises the translocation of bacteria to the lamina propria, reducing the potential for maladaptive interactions with immune cells and removing the feed-forward loop of inflammation (Spiljar et al., 2017). Second, metabolites from the gut microbiota are one of the most examined mechanisms linked to CRC prevention (Mortensen & Clausen, 1996). High production of SCFAs, specifically butyrate, has been associated with reduced CRC risk (Drummond et al., 2005; Lührs et al., 2001; Orimo et al., 2019; Peng et al., 2009; Singh et al., 2014; Thangaraju et al., 2009) and is improved with exercise (Allen, Mailing, Niemiro et al., 2018). Indeed, microbes that promote the production of SCFAs, particularly butyrate, are in low abundance in those with inflammatory bowel disease and CRC (Machiels et al., 2014; Montassier et al., 2015) and are reportedly improved with exercise. Whilst the research on SCFAs in the gut is extensive (Goodman & Gardner, 2018; Spiljar et al., 2017), briefly SCFAs have been shown to promote gut barrier health, especially the mucosal layer, providing a physical barrier between the bacteria of the gut and the vulnerable epithelial cells (Peng et al., 2009). A strong physical barrier

Table 1. Mechanistic and microbial contribution to colorectal cancer (CRC)

Subject	Mechanism	Evidence/impact/action
Pro-inflammatory cytokines		
TNF-alpha	Induce NF-kB translocation (Lührs et al., 2001)	• Mediates initiation and progression of CRC in murine models (Erdman et al., 2009; Popivanova et al., 2008)
IL-6	↑ STAT3 and NF-kB activation (Bollrath et al., 2009; Elinav et al., 2013; Grivennikov et al., 2009; Iliopoulos et al., 2009; Waldner et al., 2012)	• Early tumourigenesis • ↑ malignant tumour transformation • Feedforward amplification loop for chronic inflammation
NF-kB	Upstream promotion of inflammation (DiDonato et al., 2012; Karin & Greten, 2005; Long et al., 2017; Wang et al., 2009)	• ↑ ROS leading to ↑ DNA damage (DiDonato et al., 2012; Karin & Greten, 2005; Wang et al., 2009) • Blocks apoptosis and regulates anti-apoptosis proteins leading to ↑ survival of premalignant and malignant tumours (Barrett et al., 2015; Long et al., 2017; Myant et al., 2013)
Microbially driven CRC and CAC		
Dysbiosis	Linked to IBD, UC, and inflammation (Song et al., 2020; Vacante et al., 2020) Those with CRC and CAC present with dysbiosis (Ahn et al., 2013; Allen, Mailing, Cohrs et al., 2018; Goodman & Gardner, 2018; Montassier et al., 2015; Yu et al., 2017)	Allows for: • ↑ tumourigenic microbes (Machiels et al., 2014; Song et al., 2020) • ↑ oncogenic microbial metabolites • ↑ tumour sympathetic environment • Contributes to adenoma-carcinoma pathway (Vacante et al., 2020)
Infection	Viral and bacterial infection	• Contributes to dysbiosis
Bacterial contribution (Song et al., 2020)	*Fusobacterium nucleatum*	• Block NK cell-mediated killing of tumours via 'live and let live' hypothesis (Brennan & Garrett, 2016; Gur et al., 2015)
	Enterotoxigenic *Bacteroides fragilis*	• ↑ TH17 cell infiltration to colon leading to tumour-supportive environment (Brennan & Garrett, 2016; De Simone et al., 2013; Housseau et al., 2009)
	pks^{+} *Escherichia coli*	• ↑ presence in CRC tumours • Suggested ↑ colibactin encoding shown to potentiate CRC in mice (Arthur et al., 2014)
Gut microbiome influence on CRC via pro-inflammatory cytokines and immune modulation (Al Bander et al., 2020; Brennan & Garrett, 2016)		
↓ Gut barrier integrity	Degraded by inflammation and/or dysbiosis and infection	• ↑ LPS translocation across gut barrier • ↑ interaction of microbes with immune cells of lamina propria
↑ LPS translocation	Interacts with cells in the lamina propria and enters circulation (Brennan & Garrett, 2016; Schroeder & Bäckhed, 2016)	• ↑ unregulated immune signalling • ↑ inflammatory environment • ↑ NF-kB activation (Eberhart et al., 1994; Masuda et al., 1995; Wang & Dubois, 2010)
↑ Microbial and metabolite contact with lamina propria	Unregulated production of ROS (Sepich-Poore et al., 2021)	• ↑ mutations of cells encouraging tumourigenesis
	Influence development and function of immune cells	• ↑ interference with regulatory T cells and Th17 cells resulting in inflammation and inflammation-associated CRC (Brennan & Garrett, 2016; Chelakkot et al., 2018)

CAC, colitis-associated cancer; CRC, colorectal cancer; IBD, inflammatory bowel disorder; IL-6, interleukin-6; LPS, lipopolysaccharide; NF-kB, Nuclear factor kappa B; NK cell, natural killer cell; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcriptions 3; TH17, T helper 17 cell; TNF-alpha, tumour necrosis factor alpha; UC, ulcerative colitis.

reduces bacterial lipopolysaccharide (LPS) translocation, a key driver of inflammation and immune disruption, but also reduces the capacity for metabolites or toxins from the gut to damage epithelial cells (Al Bander et al., 2020; Peng et al., 2009). Similarly, butyrate is the preferred energy source of healthy epithelial cells and also promotes mucin formation, both of which contribute to the integrity and resilience of the mucosal barrier (Hou et al., 2022; Kim & Milner, 2007). Butyrate can inhibit LPS-mediated activation of nuclear factor kappa B (NF-kB) in cell cultures (Segain et al., 2000; Singh et al., 2014), and LPS mediated NF-kB activation is a key mechanism driving CRC development once an area of dysplasia has formed. Treatment of cancer cells with butyrate inhibits the NF-kB nuclear translocation required for initiation of many of these cascades and can significantly blunt inflammation (Karin & Greten, 2005; Lührs et al., 2001; Segain et al., 2000). Finally, butyrate has been shown to increase CRC cell death through intracellular inhibition of histone deacetylases (HDACs) (Drummond et al., 2005), and through binding to GPR109A – a receptor that initiates apoptosis in cancer cells (Singh et al., 2014; Thangaraju et al., 2009). These mechanisms linked to SCFA production in the gut are the most specific for CRC prevention primarily because of their proximity to potential tumour sites. Third, species of the gut microbiota may also reduce inflammation (Al Bander et al., 2020). As noted earlier, and although the data are correlational at this stage, decreases in *Akkermansia muciniphila* are associated with increased levels of C-reactive protein (CRP) while *Faecalibacterium* (a key butyrate producer) abundance has also been inversely correlated with levels of circulating CRP and interleukin-6 (Al Bander et al., 2020). The available data show that *Akkermansia muciniphila* and *Faecalibacterium* can be considered as bacteria of interest in relation to CRC risk. Given that exercise *per se* has been shown to independently reduce CRC risk, and also appears to positively influence each of the three characteristics discussed above, the impact(s) of exercise on the gut microbiota may be especially suited to mitigating risk of CRC.

Though the specific influence of exercise on the gut microbiome of people with CRC is yet to be examined in human trials, there are compelling data from murine models (Cook et al., 2016). Hoffman-Goetz et al. (2009) found reduced TNF-α in intestinal lymphocytes of mice that exercised. Another study found changes in the gut microbiome of sedentary germ-free mice following a fecal transplantation from active mice donors improved body composition, the metabolic profile, and reduced colonic inflammation compared to fecal transplantation from sedentary mice donors (Allen, Mailing, Cohrs et al., 2018). Mice were then exposed to dextran-sodium-sulphate (DSS) to induce colitis. Following DSS exposure, mice that had received transplants from active donors had an attenuated response to insult with comparably better preservation of the mucus layer and improved expression of cytokines involved in tissue regeneration. Interestingly, the abundances of *Akkermansia, Lachnospiraceae* and *Ruminococcus* were higher in the exercising group, which could be associated with the improved protection against colitis. The authors concluded that (i) exercise produced changes in the gut microbiome of mice, (ii) once microbiota were transferred to germ-free mice from active donors this change was significantly maintained compared to those from sedentary mice, (iii) this change alone was enough to produce phenotypical changes between groups, and (iv) mice with an active microbiota donor had an attenuated response to high dose DSS exposure compared to those who received microbiota from a sedentary donor (Allen, Mailing, Cohrs et al., 2018). While there are limitations when translating evidence from murine models to human populations, these studies do provide insights into the possible interactions between exercise, the gut microbiota and colorectal cancer risk.

Limitations of current research and future directions

The current literature contains high heterogeneity within the microbiome analysis methods and exercise prescriptions used. While this is a limitation for the specificity of the findings, the increasing volume of studies and relative consistency of the findings suggest that a range of different exercise interventions are likely to influence the gut microbiota. In a recent review that examined differences in type, intensity and duration of exercise on microbiota adaptation (Suryani et al., 2022), only one of the 10 studies included a control group (Taniguchi et al., 2018), whilst only two studies compared exercise of different intensity (Kern et al., 2020; Motiani et al., 2020) and type (Bycura et al., 2021; Morita et al., 2019). Future studies are needed to determine the optimal exercise 'dose' (including the time course of changes and maintenance of effect) to elicit changes in human gut microbiota that most favourably improve markers of health.

Several potential mechanisms linking specific bacterial infection to CRC (such as *Enterotoxigenic Bacteroides fragilis*, *Fusobacterium nucleatum* and pks$^+$ *Escherichia coli*) have not been included in the review due to insufficient available evidence that exercise may reduce the abundance of these bacteria. Further research exploring the potential influence on these and other potential CRC-risk altering bacteria are clearly warranted.

There is growing interest in the gut–muscle axis (Burtscher et al., 2022). Myokines produced by exercising muscle have been implicated in reducing cancer risk (Badal et al., 2020; Lochlainn et al., 2018; Shin et al., 2019; Ticinesi et al., 2017; Ticinesi et al., 2019; Watson et al., 2021). Furthermore, lean mass is related to butyrate

production and seemingly positive shifts in microbiota characteristics (Allen, Mailing, Niemiro et al., 2018). Indeed, a recent study found that induced dysbiosis in mice blunted hypertrophy compared to mice with a 'normal' microbiome (Valentino et al., 2021). Therefore, the gut–muscle axis may very well be important to maximising the benefits of a gut microbiota-targeted exercise intervention, especially in those experiencing dysbiosis following treatment.

Though this review has focused primarily on the relationship between exercise-mediated changes to the gut microbiome and CRC risk, the proposed improvements in immune function and reductions in inflammation may also reduce the risk of developing other chronic diseases that are more likely following a diagnosis of and treatment for CRC, including other cancers. Similarly, the microbiota may be of interest in research targeting optimisation of recovery from cancer treatments. Finally, and although diet as a possible intervention for reducing CRC risk and/or recovery has long been considered (Zhou & Rifkin, 2021), future research should examine the potential for combined diet and exercise interventions to reduce cancer risk via changes to the gut microbiome.

Conclusion

Though exercise has long been associated with a reduced risk of CRC, the mechanisms underpinning this relationship are not clear. An established connection between the bacterial component of the human gut microbiome and colorectal cancer is present, with certain microbial products and activities contributing to risk of tumour development while other traits are protective against colorectal cancer. Recent evidence shows an interaction between exercise and the gut microbiota that appears to support changes in the microbiota that theoretically reduce cancer risk, and may explain, at least in part, the inverse associations seen with exercise and CRC. Exercise-mediated changes to the gut microbiota can improve the immune system and reduce systematic inflammation, both of which are known to influence CRC risk. More specifically, the exercise literature suggests that the diversity and relative abundance of certain microbes, particularly those bacterial taxa that produce butyrate, are enhanced with exercise and when compared to the microbiota-CRC literature, appears to be the inverse of pro-CRC microbiota characteristics. Thereby, it is proposed that exercise mediated changes in the gut microbiota may link to both reducing risk of CRC and supporting microbial protection against tumour formation. However, much of our knowledge in these areas is still restricted to bacteria, with much to be learned about how other members of the gut microbiota (fungi, archaea, viruses) are implicated in this exciting area for research, and to further establish the mechanisms and subsequent optimal prescription to reduce the risk of CRC.

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Additional information

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None.

Author contributions

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