



WITH DR. TOM O'BRYAN

Unintended Sabotage

When '*Healthy Diets*' Increase Morbidity and Mortality

HEALCON 2024



© www.theDr.com

Tom O'Bryan, DC, CCN, DACBN, CIFM

- ***President, Swiss Mountain Academy***
- ***Adjunct Faculty - The Institute for Functional Medicine***
- ***Adjunct Faculty - The National University of Health Sciences***
- ***Adjunct Faculty - Integrative and Functional Nutrition Academy***
- ***Chief Medical Officer - Sun Horse Energy***
- ***Clinical Consultant on Functional Medicine - NuMedica, Inc.***
- ***Clinical Consultant on Functional Medicine - Vibrant America***
- ***Editorial Review Board - Alternative Therapies in Health and Medicine***
- ***Editorial Review Board - Journal of International Medicine***
- ***Medical Advisory Board - L-Nutra. llc***
- ***Medical Advisory Board - GetHealthy.store***
- ***Medical Advisory Board - Functional Medicine Coaching Academy***
- ***Medical Advisory Board - Functional Medicine University***
- ***Medical Advisory Board - Cancer Schmancer***
- ***Medical Advisory Board - Mios, LLC***
- ***Medical Advisory Board - Institute for Functional Nutrition***
- ***Medical Advisory Board - Nutritional Therapy Association***
- ***Medical Advisory Board - National Association of Nutritional Professionals***
- ***Medical Advisory Board - Association of Natural Health***
- ***International Scientific Advisory Board - Daivam Wellness Pvt Ltd.***
- ***Scientific Advisory Board - International and American Association of Clinical Nutritionists***



Big Boss





Premise #1

***“Medical science has made such tremendous progress
that there is hardly a healthy human left.”***

Aldous Huxley



Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity?

Niharika A. Duggal¹, Grace Niemi², Stephen D. R. Harridge³, Richard J. Simpson^{2,4,5} and Janet M. Lord^{1,6*}

Abstract | Remodelling of the immune system with age — immunosenescence — is a substantial contributor to poor health in older adults, with increasing risk of infections, cancer and chronic inflammatory disease contributing to age-related multi-morbidity. What is seldom considered

Between 1990 and 2010, life expectancy increased by 4.2 years in men and 1.9 years in women, but healthy life expectancy did not keep pace, increasing at approximately half this rate

¹MRC-ARUK Centre for Musculoskeletal Ageing Research, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.

²Department of Pediatrics, University of Arizona, Tucson, AZ, USA.

³Centre for Human and Applied Physiological Sciences, King's College London, London, UK.

⁴Department of Nutritional Sciences, University of Arizona, Tucson, AZ, USA.

⁵Department of Immunobiology, University of Arizona, Tucson, AZ, USA.

⁶NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham, Birmingham, UK.

*e-mail: j.m.lord@bham.ac.uk
<https://doi.org/10.1038/s41577-019-0177-9>

countries: between 1990 and 2010, life expectancy in the United Kingdom increased by 4.2 years in men and 1.9 years in women, but healthy life expectancy did not keep pace, increasing at approximately half this rate¹. We are thus living longer, but not healthier. Furthermore, ill health in old age is typically not due to any one disease but, instead, many older adults are multi-morbid — defined here as the presence of two or more chronic conditions. For example, in a retrospective study of disease incidence in Minnesota, USA, from 2005 to 2010, 22% of adult patients overall had two or more conditions, and this number rose to 77% in the over 65-year-old group². Understanding the drivers of age-related multi-morbidity and developing interventions to prevent or delay its occurrence are now priorities in many countries.

It is often not appreciated that increased population longevity is a relatively recent phenomenon, beginning around 250 years ago³. This is a relatively short time in the context of our genetic heritage, in which our global physiology and accompanying immune system evolved to meet the demands of an active hunter-gatherer lifestyle⁴ (FIG. 1). Our modern lifestyle goes against the blueprint laid down by this genetic inheritance, with

multi-morbidity and increased incidence of cardiovascular disease, obesity, type 2 diabetes and cancer⁵. Thus, it is becoming increasingly clear that being sufficiently physically active across the life course is a central requirement for achieving a healthy old age⁶. Moderate-to-vigorous physical activity and cardiorespiratory fitness are both key predictors for reduced all-course mortality^{6,9}, and the reverse is true for sedentary behaviour, such as sitting or lying down^{10,11}. Indeed, large-cohort studies have revealed that physical activity and time spent being sedentary are independent variables affecting health and that the ideal is to maintain adequate levels of physical activity and minimize sedentary time¹¹. Unfortunately, physical activity tends to decline dramatically with age. For instance, less than 10% of UK adults aged over 65 years meet the Chief Medical Officer's recommendation for physical activity of 150 minutes of aerobic exercise a week. Furthermore, as the immune system is readily influenced by physical activity¹², increased inactivity across the lifespan may also contribute to reduced immunity in old age.

In this Review, we discuss the evidence suggesting that reduced physical activity with age is a major contributor to age-related immune decline, which in turn



Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity?

Niharika A. Duggal¹, Grace Niemi², Stephen D. R. Harridge³, Richard J. Simpson^{2,4,5} and Janet M. Lord^{1,6*}

Abstract | Remodelling of the immune system with age — immunosenescence — is a substantial contributor to poor health in older adults, with increasing risk of infections, cancer and chronic inflammatory disease contributing to age-related multi-morbidity. What is seldom considered when examining the immune response of an aged individual is that the immune system is profoundly influenced by physical activity. Habitual physical activity levels decline with age, with significant consequences for muscle mass and function. Skeletal muscle is a major immune regulatory organ and generates a range of proteins, termed myokines, which have anti-inflammatory and immunoprotective effects. Several studies indicate that maintaining physical

We are thus living longer, but not healthier.

Whether physical activity could improve immunotherapy outcomes in age-related conditions such as cancer.

There is a continuing trend for increased human life expectancy across the globe, particularly in developed countries¹. Between 1990 and 2010, life expectancy in the United Kingdom increased by 4.2 years in men and 1.9 years in women, but healthy life expectancy did not keep pace, increasing at approximately half this rate². We are thus living longer, but not healthier. Furthermore, ill health in old age is typically not due to any one disease but, instead, many older adults are multi-morbid — defined here as the presence of two or more chronic conditions. For example, in a retrospective study of disease incidence in Minnesota, USA, from 2005 to 2010, 22% of adult patients overall had two or more conditions, and this number rose to 77% in the over 65-year-old group³. Understanding the drivers of age-related multi-morbidity and developing interventions to prevent or delay its occurrence are now priorities in many countries.

It is often not appreciated that increased population longevity is a relatively recent phenomenon, beginning around 250 years ago⁴. This is a relatively short time in the context of our genetic heritage, in which our global physiology and accompanying immune system evolved to meet the demands of an active hunter-gatherer lifestyle⁵ (FIG. 1). Our modern lifestyle goes against the blueprint laid down by this genetic inheritance, with

inactivity and overeating resulting in impaired function across a range of systems in old age⁶, culminating in multi-morbidity and increased incidence of cardiovascular disease, obesity, type 2 diabetes and cancer⁶. Thus, it is becoming increasingly clear that being sufficiently physically active across the life course is a central requirement for achieving a healthy old age⁷. Moderate-to-vigorous physical activity and cardiorespiratory fitness are both key predictors for reduced all-course mortality^{8,9}, and the reverse is true for sedentary behaviour, such as sitting or lying down^{10,11}. Indeed, large-cohort studies have revealed that physical activity and time spent being sedentary are independent variables affecting health and that the ideal is to maintain adequate levels of physical activity and minimize sedentary time¹¹. Unfortunately, physical activity tends to decline dramatically with age. For instance, less than 10% of UK adults aged over 65 years meet the Chief Medical Officer's recommendation for physical activity of 150 minutes of aerobic exercise a week. Furthermore, as the immune system is readily influenced by physical activity¹², increased inactivity across the lifespan may also contribute to reduced immunity in old age.

In this Review, we discuss the evidence suggesting that reduced physical activity with age is a major contributor to age-related immune decline, which in turn

¹MRC-ARUK Centre for Musculoskeletal Ageing Research, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.

²Department of Pediatrics, University of Arizona, Tucson, AZ, USA.

³Centre for Human and Applied Physiological Sciences, King's College London, London, UK.

⁴Department of Nutritional Sciences, University of Arizona, Tucson, AZ, USA.

⁵Department of Immunobiology, University of Arizona, Tucson, AZ, USA.

⁶NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham, Birmingham, UK.

*e-mail: j.m.lord@bham.ac.uk

<https://doi.org/10.1038/s41577-019-0177-9>



Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity?

Niharika A. Duggal¹, Grace Niemi², Stephen D. R. Harridge³, Richard J. Simpson^{2,4,5} and Janet M. Lord^{1,6*}

Abstract | Remodelling of the immune system with age — immunosenescence — is a substantial contributor to poor health in older adults, with increasing risk of infections, cancer and chronic inflammatory disease contributing to age-related multi-morbidity. What is seldom considered when examining the immune response of an aged individual is that the immune system is profoundly influenced by physical activity. Habitual physical activity levels decline with age,

Ill health in old age is typically not due to any one disease but, instead, many older adults are multi-morbid — defined here as the presence of two or more chronic conditions.

There is a continuing trend for increased human life expectancy across the globe, particularly in developed countries¹. Between 1990 and 2010, life expectancy in the United Kingdom increased by 4.2 years in men and 1.9 years in women, but healthy life expectancy did not keep pace, increasing at approximately half this rate². We are thus living longer, but not healthier. Furthermore, ill health in old age is typically not due to any one disease but, instead, many older adults are multi-morbid — defined here as the presence of two or more chronic conditions. For example, in a retrospective study of disease incidence in Minnesota, USA, from 2005 to 2010, 22% of adult patients overall had two or more conditions, and this number rose to 77% in the over 65-year-old group³. Understanding the drivers of age-related multi-morbidity and developing interventions to prevent or delay its occurrence are now priorities in many countries.

It is often not appreciated that increased population longevity is a relatively recent phenomenon, beginning around 250 years ago⁴. This is a relatively short time in the context of our genetic heritage, in which our global physiology and accompanying immune system evolved to meet the demands of an active hunter-gatherer lifestyle⁵ (Fig. 1). Our modern lifestyle goes against the blueprint laid down by this genetic inheritance, with

inactivity and overeating resulting in impaired function across a range of systems in old age⁶, culminating in multi-morbidity and increased incidence of cardiovascular disease, obesity, type 2 diabetes and cancer⁶. Thus, it is becoming increasingly clear that being sufficiently physically active across the life course is a central requirement for achieving a healthy old age⁷. Moderate-to-vigorous physical activity and cardiorespiratory fitness are both key predictors for reduced all-course mortality^{8,9}, and the reverse is true for sedentary behaviour, such as sitting or lying down^{10,11}. Indeed, large-cohort studies have revealed that physical activity and time spent being sedentary are independent variables affecting health and that the ideal is to maintain adequate levels of physical activity and minimize sedentary time¹¹. Unfortunately, physical activity tends to decline dramatically with age. For instance, less than 10% of UK adults aged over 65 years meet the Chief Medical Officer's recommendation for physical activity of 150 minutes of aerobic exercise a week. Furthermore, as the immune system is readily influenced by physical activity¹², increased inactivity across the lifespan may also contribute to reduced immunity in old age.

In this Review, we discuss the evidence suggesting that reduced physical activity with age is a major contributor to age-related immune decline, which in turn

¹MRC-ARUK Centre for Musculoskeletal Ageing Research, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.

²Department of Pediatrics, University of Arizona, Tucson, AZ, USA.

³Centre for Human and Applied Physiological Sciences, King's College London, London, UK.

⁴Department of Nutritional Sciences, University of Arizona, Tucson, AZ, USA.

⁵Department of Immunobiology, University of Arizona, Tucson, AZ, USA.

⁶NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham, Birmingham, UK.

*e-mail: j.m.lord@bham.ac.uk
https://doi.org/10.1038/s41577-019-0177-9



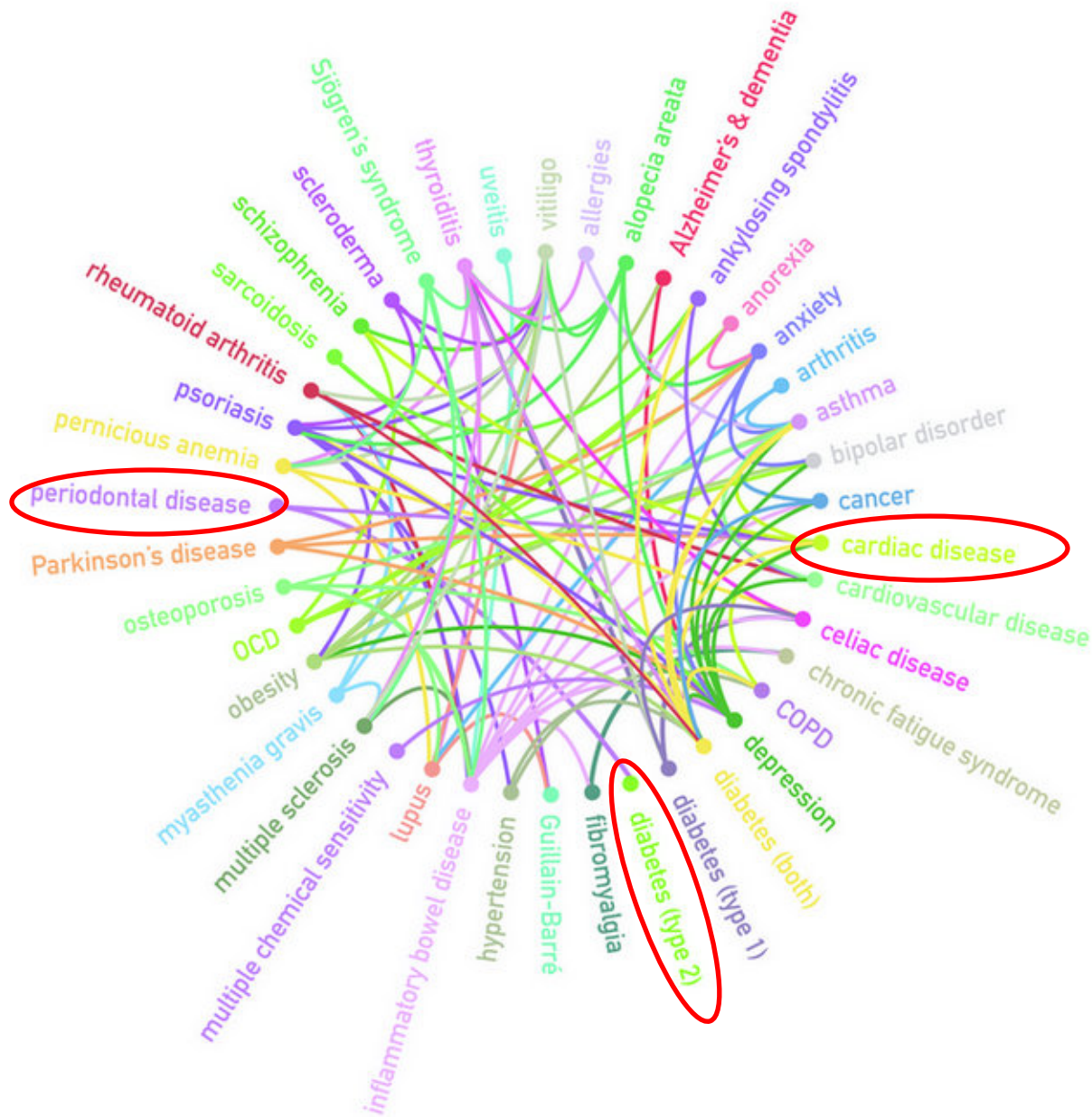


Figure 1. Comorbidities among common inflammatory diseases. Each 'spoke' of this wheel represents a published study appearing in MEDLINE, which shows a significant statistical relationship between one disease and another.

[Home](#)

[Business, industry
and trade](#)

[Economy](#)

[Employment and
labour market](#)

[People, population
and community](#)

[Taking part in a
survey?](#)

Search for a keyword(s) or time series ID



census 2021 [Data and analysis from Census 2021](#)

[Home](#) > [Release calendar](#) > [Published](#) >

Health state life expectancies in England, Northern Ireland and Wales: between 2011 to 2013 and 2020 to 2022

For the three aggregated years 2020–22, with male life expectancy was 78.8 years, average healthy male life expectancy was only 62.4 years – ie, 16.4 of those years (21%) would have been spent in poor health.



Care team

Contact:
[Ageing, Disability and Social](#)

Release date:
26 March 2024 09:30

Next release:
To be announced

[Home](#)

[Business, industry
and trade](#)

[Economy](#)

[Employment and
labour market](#)

[People, population
and community](#)

[Taking part in a
survey?](#)

Search for a keyword(s) or time series ID



census 2021 [Data and analysis from Census 2021](#)

[Home](#) > [Release calendar](#) > [Published](#) >

Female life expectancy was 82.8 years, of which 20.1 years (24%) would have been spent in poor health. Although females live an average of four years longer than males, they spend a higher proportion and more years of their lives in poor health.

England and Wales: between 2011 to 2013 and 2020 to 2022



Care team

Contact:
[Ageing, Disability and Social](#)

Release date:
26 March 2024 09:30

Next release:
To be announced

[Home](#)

[Business, industry
and trade](#)

[Economy](#)

[Employment and
labour market](#)

[People, population
and community](#)

[Taking part in a
survey?](#)

Search for a keyword(s) or time series ID



census2021 [Data and analysis from Census 2021](#)

[Home](#) > [Release calendar](#) > [Published](#) >

Disability-free life expectancy is almost two decades shorter than life expectancy, and is higher among males (61.8 years) than females (60.5 years).

Health state life expectancies in England, Northern Ireland and Wales: between 2011 to 2013 and 2020 to 2022



Care team

Contact:

[Ageing, Disability and Social](#)

Release date:

26 March 2024 09:30

Next release:

To be announced



In my Clinical Experience, No One Gets 1 Disease. They May Get 1 Diagnosis, But The Mechanism is Systemic. And the Result of this?



For different autoimmune conditions, incidence is increasing at ranges between 3% and 9% year on year.

This includes:

7.0% increase per year of rheumatic diseases (RA)

**6.3% increase of endocrinological conditions such as
type 1 diabetes**

3.7% increase of neurological such as MS

4–9% a year for Coeliac Disease

increasing in incidence by as much as 9% each year – potentially meaning further increased costs in the future. Medical science does not yet know the reason for the rise, and the charities are campaigning for change in the way research is approached.

Chloe Gillum, 25, is a paediatric nurse who lives with three autoimmune conditions. At the age of nine she was diagnosed with type 1 diabetes and went on to develop vitiligo and an underactive thyroid, which caused secondary Raynaud's. The autoimmune conditions all need daily medication which requires management, patience and discipline, but as Chloe explains: "One of the hardest things about living with autoimmune conditions is people not understanding the impact this has on my life."



“Wake Up!!!”



Pandemic of idiopathic multimorbidity

Stephen J. Genuis MD FRSC DABOG DABEM

*There are two ways to be fooled:
One is to believe what isn't so; the other is to refuse to
believe what is so.*

Søren Kierkegaard

Sitting among colleagues in the private room of a swank eatery, I recently had the pleasure of participating in a pharmaceutical industry-sponsored medical education event allegedly exploring the management of patients presenting to their health providers with multisystem health complaints. The amateur for the evening—an eloquent orator with impressive credentials—raised the issue of the rising prevalence of patients who present with a laundry list of ongoing and seemingly

we were apprised of a likely genetic source—a perplexing supposition considering the marked increase in the prevalence of multimorbidity and, to my knowledge, the lack of a widespread mutation of the population gene pool. However, at my table, one particularly erudite medico imbued with the wisdom of vino simply said of such patients, “I think they’re all nuts.”

Background

The simultaneous coexistence of ongoing multisystem health complaints in a single person—sometimes referred to as *multimorbidity*—often presents a difficult clinical situation for physicians.^{6,7} In this month's issue of *Canadian Family Physician* (page 533), Tymchak and

***There are two ways to be fooled:
One is to believe what isn't so;
the other is to refuse to believe what is so.***

Søren Kierkegaard

colonic intervention. Although not specifically classified in the sacrosanct *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, this affliction—we were told—is a manifestation of depression and requires antidepressant therapy whether or not melancholy is evident. Furthermore, failure to treat early and vigorously would likely be “depressogenic” via neuroplastic mechanisms of laying down pathophysiological pathways biochemically destined to induce chronicity and ongoing somatic health complaints.³ In addition to clinical depression, some of these patients apparently also qualify for the forthcoming *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, new diagnosis of somatic symptoms disorder,⁴ which, unsurprisingly, might be treated in some situations with antidepressant medication.⁵ When asked about the underlying origins of this clinical presentation,

care they typically receive?

The expanding challenge of this type of multimorbidity is profoundly important for patients and the medical system.^{7,10} When primary care practitioners find nothing to account for the various symptoms and have little to offer in terms of solutions, patients typically experience frustration and do not know how to proceed. Follow-up visits often result in referral to assorted specialists who generally focus on one component of the patient's problem—the neurologist explores recurrent headaches and brain fog, the gastroenterologist assesses abdominal discomfort, the rheumatologist evaluates the fibromyalgia, and so on. When serial consultations result in a lack of objective findings, psychiatric referral is often suggested. Presented with this recommendation, disgruntled patients sometimes lose faith in the acumen of their physicians and often end up frequenting the establishments of alternative practitioners, which accounts for the sobering reality that there are more visits in the United States to nonconventional health practitioners than to primary care physicians.¹⁵

This article has been peer reviewed. *Can Fam Physician* 2014;60:511-4.

La traduction en français de cet article se trouve à www.cfp.ca dans la table des matières du numéro de juin 2014 à la page e290.





The answer is 17 years, what is the question: understanding time lags in translational research

Zoë Slote Morris¹ • Steven Wooding² • Jonathan Grant²

¹Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK

²RAND Europe, Cambridge CB4 1YG, UK

Correspondence to: Jonathan Grant. Email: jgrant@rand.org

DECLARATIONS

Competing interests

None declared

Funding

This is an independent paper

Summary

This study aimed to review the literature describing and quantifying time lags in the health research translation process. Papers were included in the review if they quantified time lags in the development of health interventions. The study identified 23 papers. Few were comparable as different studies use different measures, of different things, at different time points. We concluded that the current state of knowledge of time lags

It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.

Ethical approval

Not applicable

Guarantor

JG

Contributorship

ZSM designed, conducted and analysed the literature review, and drafted and revised the paper; JG initiated the project, drafted and revised the paper, and has led a number of studies cited that attempted to measure lags; SW revised the paper

Timely realization of the benefits of expensive medical research is an international concern attracting considerable policy effort around 'translation'.^{1,2} Policy interventions to improve translation respond to a vast empirical literature on the difficulties of getting research across research phases and into practice.^{3–11}

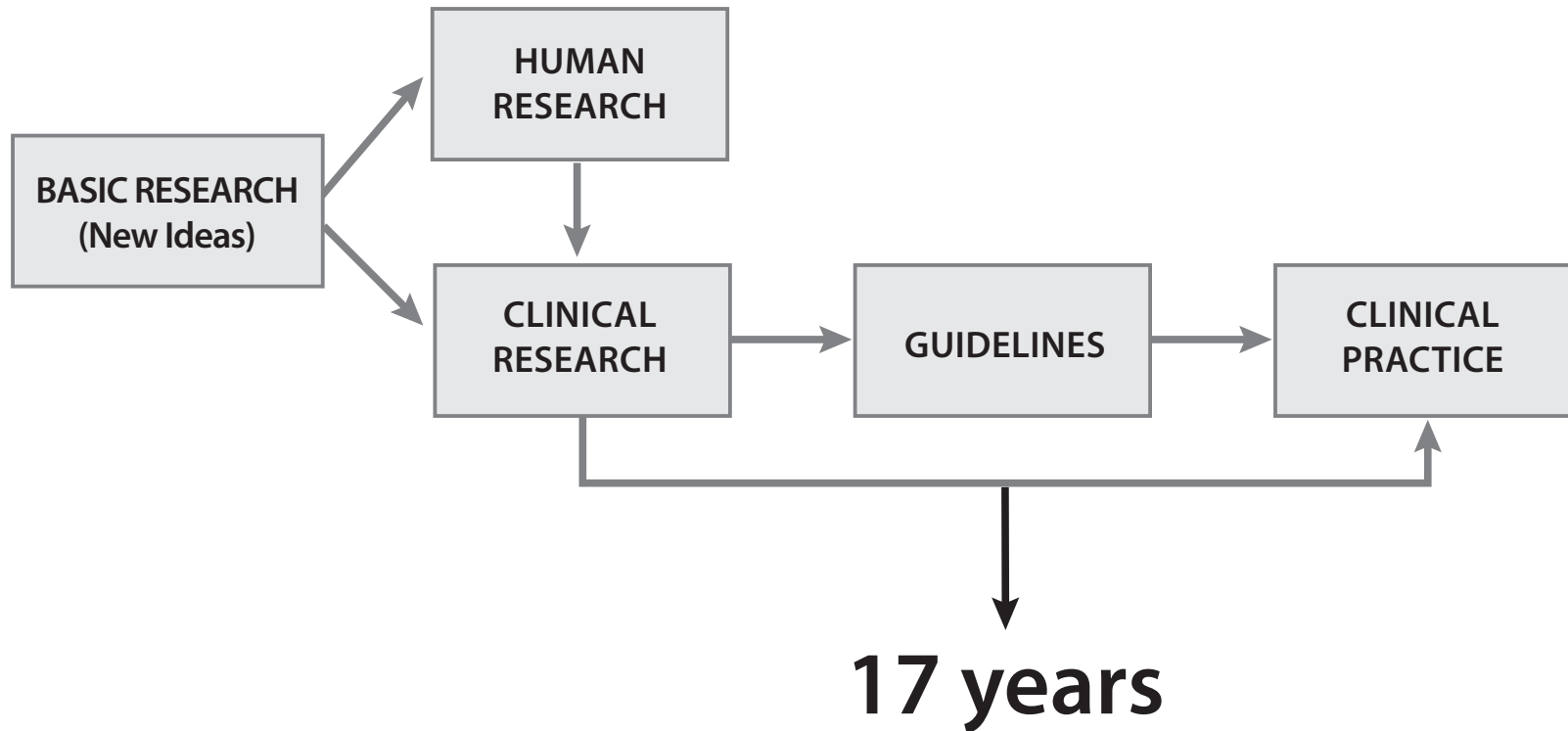
Both literature and policy tend to assume that speedy translation of research into practice is a good thing. Delays are seen as a waste of scarce resources and a sacrifice of potential patient benefit.¹² Although some lag will be necessary to ensure the safety and efficacy of new interventions or advances, in essence we should aim to optimize lags. One recent study (of which JG and SW were co-authors) estimating the economic benefit of cardiovascular disease (CVD) research in the UK between 1975 and 2005, found an internal rate of return (IRR) of CVD research of 39%.¹³ In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits

Of this, 9% was attributable to the benefit from health improvements, which is the focus of this paper. (The remaining 30% arise from 'spillovers' benefiting the wider economy.) This level of benefit was calculated using an estimated lag of 17 years. Varying the lag time from 10 to 25 years produced rates of return of 13% and 6%, respectively, illustrating that shortening the lag between bench and bedside improves the overall benefit of cardiovascular research. What is notable is that all the above calculations depended upon an estimated time lag; estimated because, despite longstanding concerns about them,¹⁴ time lags in health research are little understood.

It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.^{1,3,15} Balas and Bohen,¹⁶ Grant¹⁷ and Wratschko¹⁸ all estimated a time lag of 17 years measuring different points of the process. Such convergence around an 'average' time lag of 17 years hides complexities that are relevant to



450 The answer is 17 years, what is the



It takes an average of 17 years for basic science research to be used by your doctor.

...the project, drafted and revised the paper, and has led a number of studies cited that attempted to measure lags; SW revised the paper

of advances, in essence we should aim to optimize lags. One recent study (of which JG and SW were co-authors) estimating the economic benefit of cardiovascular disease (CVD) research in the UK between 1975 and 2005, found an internal rate of return (IRR) of CVD research of 39%.¹³ In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits

understood.

It is frequently stated that it takes an average of 17 years for research evidence to reach clinical practice.^{1,3,15} Balas and Bohen,¹⁶ Grant¹⁷ and Wratschko¹⁸ all estimated a time lag of 17 years measuring different points of the process. Such convergence around an 'average' time lag of 17 years hides complexities that are relevant to



What does it take to put an ugly fact through the heart of a beautiful hypothesis?

Thomas Huxley characterized “the great tragedy of Science” as “the slaying of a beautiful hypothesis by an ugly fact.”

Unfortunately, when medical hypotheses are disproved, they act more like zombies than corpses, revived by the sorcerers of Mammon, aided and abetted by the inertia of medical practice.

Recent examples in diverse areas of clinical practice will likely suffer the problem of perseverance of beautiful but flawed hypotheses, so we are raising the alarm now. 3 large trials in 2008 showed that intensive control of type 2 diabetes mellitus lacks benefits for patients and increases adverse effects (1-3), and 2 trials showed that self-monitoring of blood sugar in type 2 diabetes is not cost-effective (4) and is associated with depression (5). 2 trials have documented the lack of benefits of antiviral agents for Bell palsy (while confirming the benefits of corticosteroids) (6, 7), one of which (6) is featured in this issue of *ACP Journal Club* (8).

Can we do no better than this in medicine? Apparently not. A recent study documents the persistence of outmoded claims in the medical literature (15). Quality-of-care studies show that our profession is always behind the evidence curve, with < 50% adoption of validated new procedures many years after the evidence has become clear. Worse still, studies show that didactic instruction, still the predominant method of continuing education, has no discernable effect on clinical practice, and practitioners are quite resistant to seemingly vigorous interventions, such as audit and feedback, preceptorships, patient-mediated interventions, educational influentials, and computerized decision support (16, 17).

What does it take to put an ugly fact through the heart of a beautiful hypothesis? Clearly, facts by themselves are not enough or at least not fast enough. Individually, we need to do what we can in our own practices. For type 2 diabetes, the recent trials mean backing off trying to help patients reach the “goal” of

At the turn of the 20th century, renowned physicist Max Planck remarked, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with the new truth.”

does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it.”

In more modern times, social psychologists have empirically studied people's tendency to cling to cherished beliefs, even in the face of a mountain of disconfirming evidence, known formally as confirmation bias. Once a belief is established, people will actively seek out information that supports it. If confronted with mixed evidence, people will give greater weight to information that supports their belief while discounting contradictory information. For instance, in 1 experiment, both foes and proponents of capital punishment were presented with an empirical report that either concluded that capital punishment was effective or ineffective. When the conclusion did not support their beliefs, both those for and against capital punishment were hasty to point out methodological flaws of the research design and found the results unconvincing. When the conclusion supported their beliefs, however, people praised the research for its sound design (14).

there are legitimate and important research questions about research translation. Ironically, the attitudes of some members of the research community—that we simply need to try harder at broadcasting our research and that translation research is not needed, let alone legitimate—has been slow to change. However, it is changing, and a cohort of KT researchers is emerging.

When will we be able to slay beautiful hypotheses more efficiently? No one knows, but at least KT research is becoming fashionable and is beginning to address the right questions. Meanwhile, if the new evidence differs from the advice you have been giving your patients about antiviral agents for Bell palsy, intensive care for type 2 diabetes, or antioxidants for preventing cancer or cardiovascular disease, it is time to consider revising your practice. According to Pathman and colleagues (19), the logical steps for this include becoming aware of the evidence (awareness), agreeing with it in principle (agreement), deciding that it is appropriate and feasible to use in your own practice (adoption), and finally succeeding in following it at appropriate times (adherence)—a model that is consistent with guideline implementation for hypertension management in primary care settings (20).



What does it take to put an ugly fact through the heart of a beautiful hypothesis?

Thomas Huxley characterized “the great tragedy of Science” as “the slaying of a beautiful hypothesis by an ugly fact.”

Unfortunately, when medical hypotheses are disproved, they act more like zombies than corpses, revived by the sorcerers of Mammon, aided and abetted by the inertia of medical practice.

Recent examples in diverse areas of clinical practice will likely suffer the problem of perseverance of beautiful but flawed hypotheses, so we are raising the alarm now. 3 large trials in 2008 showed that intensive control of type 2 diabetes mellitus lacks benefits for patients and increases adverse effects (1-3), and 2 trials showed that self-monitoring of blood sugar in type 2 diabetes is not cost-effective (4) and is associated with depression (5). 2 trials have documented the lack of benefits of antiviral agents for Bell palsy (while confirming the benefits of corticosteroids) (6, 7), one of which (6) is featured in this issue of *ACP Journal Club* (8). Many trials and meta-analyses have confirmed and reconfirmed the absence of benefits and presence of harmful effects of antioxidants for the prevention of cancer (9, 10) and cardiovascular

Can we do no better than this in medicine? Apparently not. A recent study documents the persistence of outmoded claims in the medical literature (15). Quality-of-care studies show that our profession is always behind the evidence curve, with < 50% adoption of validated new procedures many years after the evidence has become clear. Worse still, studies show that didactic instruction, still the predominant method of continuing education, has no discernable effect on clinical practice, and practitioners are quite resistant to seemingly vigorous interventions, such as audit and feedback, preceptorships, patient-mediated interventions, educational influentials, and computerized decision support (16, 17).

What does it take to put an ugly fact through the heart of a beautiful hypothesis? Clearly, facts by themselves are not enough or at least not fast enough. Individually, we need to do what we can in our own practices. For type 2 diabetes, the recent trials mean backing off trying to help patients reach the “goal” of HbA_{1c} levels < 7% and, if they are not on insulin or prone to hypoglycemia, not advising glucose self-monitoring unless they request it. It is not clear whether the glycemic goal should be

Once a belief is established, people will actively seek out information that supports it. If confronted with mixed evidence, people will give greater weight to information that supports their belief while discounting contradictory information

renowned physicist Max Planck remarked, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it.”

In more modern times, social psychologists have empirically studied people's tendency to cling to cherished beliefs, even in the face of a mountain of disconfirming evidence, known formally as confirmation bias. Once a belief is established, people will actively seek out information that supports it. If confronted with mixed evidence, people will give greater weight to information that supports their belief while discounting contradictory information. For instance, in 1 experiment, both foes and proponents of capital punishment were presented with an empirical report that either concluded that capital punishment was effective or ineffective. When the conclusion did not support their beliefs, both those for and against capital punishment were hasty to point out methodological flaws of the research design and found the results unconvincing. When the conclusion supported their beliefs, however, people praised the research for its sound design (14).

efficiently translate research from 1 level to the next and that there are legitimate and important research questions about research translation. Ironically, the attitudes of some members of the research community—that we simply need to try harder at broadcasting our research and that translation research is not needed, let alone legitimate—has been slow to change. However, it is changing, and a cohort of KT researchers is emerging.

When will we be able to slay beautiful hypotheses more efficiently? No one knows, but at least KT research is becoming fashionable and is beginning to address the right questions. Meanwhile, if the new evidence differs from the advice you have been giving your patients about antiviral agents for Bell palsy, intensive care for type 2 diabetes, or antioxidants for preventing cancer or cardiovascular disease, it is time to consider revising your practice. According to Pathman and colleagues (19), the logical steps for this include becoming aware of the evidence (awareness), agreeing with it in principle (agreement), deciding that it is appropriate and feasible to use in your own practice (adoption), and finally succeeding in following it at appropriate times (adherence)—a model that is consistent with guideline implementation for hypertension management in primary care settings (20).



What does it take to put an ugly fact through the heart of a beautiful hypothesis?

Thomas Huxley characterized “the great tragedy of Science” as “the slaying of a beautiful hypothesis by an ugly fact.”

Unfortunately, when medical hypotheses are disproved, they act more like zombies than corpses, revived by the sorcerers of Mammon, aided and abetted by the inertia of medical practice.

Recent examples in diverse areas of clinical practice will likely suffer the problem of perseverance of beautiful but flawed hypotheses, so we are raising the alarm now. 3 large trials in 2008 showed that intensive control of type 2 diabetes mellitus lacks benefits for patients and increases adverse effects (1-3), and 2 trials showed that self-monitoring of blood sugar in type 2 diabetes is not cost-effective (4) and is associated with depression (5). 2 trials have documented the lack of benefits of antiviral agents for Bell palsy (while confirming the benefits of corticosteroids) (6, 7), one of which (6) is featured in this issue of *ACP Journal Club* (8). Many trials and meta-analyses have confirmed and reconfirmed the absence of benefits and presence of harmful effects of anti-

Can we do no better than this in medicine? Apparently not. A recent study documents the persistence of outmoded claims in the medical literature (15). Quality-of-care studies show that our profession is always behind the evidence curve, with < 50% adoption of validated new procedures many years after the evidence has become clear. Worse still, studies show that didactic instruction, still the predominant method of continuing education, has no discernable effect on clinical practice, and practitioners are quite resistant to seemingly vigorous interventions, such as audit and feedback, preceptorships, patient-mediated interventions, educational influentials, and computerized decision support (16, 17).

What does it take to put an ugly fact through the heart of a beautiful hypothesis? Clearly, facts by themselves are not enough or at least not fast enough. Individually, we need to do what we can in our own practices. For type 2 diabetes, the recent trials mean backing off trying to help patients reach the “goal” of HbA_{1c} levels < 7% and, if they are not on insulin or prone to hypoglycemia, not advising glucose self-monitoring unless they

Quality-of-care studies show that the medical profession is always behind the evidence curve, with < 50% adoption of validated new procedures many years after the evidence has become clear.

they are too strong to be broken.” At the turn of the 20th century, renowned physicist Max Planck remarked, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die and a new generation grows up that is familiar with it.”

In more modern times, social psychologists have empirically studied people’s tendency to cling to cherished beliefs, even in the face of a mountain of disconfirming evidence, known formally as confirmation bias. Once a belief is established, people will actively seek out information that supports it. If confronted with mixed evidence, people will give greater weight to information that supports their belief while discounting contradictory information. For instance, in 1 experiment, both foes and proponents of capital punishment were presented with an empirical report that either concluded that capital punishment was effective or ineffective. When the conclusion did not support their beliefs, both those for and against capital punishment were hasty to point out methodological flaws of the research design and found the results unconvincing. When the conclusion supported their beliefs, however, people praised the research for its sound design (14).

recognizes our insufficient knowledge of how to effectively and efficiently translate research from 1 level to the next and that there are legitimate and important research questions about research translation. Ironically, the attitudes of some members of the research community—that we simply need to try harder at broadcasting our research and that translation research is not needed, let alone legitimate—has been slow to change. However, it is changing, and a cohort of KT researchers is emerging.

When will we be able to slay beautiful hypotheses more efficiently? No one knows, but at least KT research is becoming fashionable and is beginning to address the right questions. Meanwhile, if the new evidence differs from the advice you have been giving your patients about antiviral agents for Bell palsy, intensive care for type 2 diabetes, or antioxidants for preventing cancer or cardiovascular disease, it is time to consider revising your practice. According to Pathman and colleagues (19), the logical steps for this include becoming aware of the evidence (awareness), agreeing with it in principle (agreement), deciding that it is appropriate and feasible to use in your own practice (adoption), and finally succeeding in following it at appropriate times (adherence)—a model that is consistent with guideline implementation for hypertension management in primary care settings (20).



Are you Going to be the Change?







Premise #2

Where Do We Begin Educating Our Patients?





**Although it is naive to claim a '*root cause*' to disease,
there is a common root *mechanism* in the
development of every Chronic Disease.**



The 15 leading causes of death in 2019 were:

- 
1. Diseases of heart (heart disease)
 2. Malignant neoplasms (cancer)
 3. Accidents (unintentional injuries)
 4. Chronic lower respiratory diseases
 5. Cerebrovascular diseases (stroke)
 6. Alzheimer disease
 7. Diabetes mellitus (diabetes)
 8. Nephritis, nephrotic syndrome and nephrosis (kidney disease)
 9. Influenza and pneumonia
 10. Intentional self-harm (suicide)
 11. Chronic liver disease and cirrhosis
 12. Septicemia
 13. Essential hypertension and hypertensive renal disease (hypertension)
 14. Parkinson disease
 15. Pneumonitis due to solids and liquids





Published in final edited form as:

Nat Med. 2019 December ; 25(12): 1822–1832. doi:10.1038/s41591-019-0675-0.

Chronic inflammation in the etiology of disease across the life span

David Furman^{1,2,3,4,*}, Judith Campisi^{1,5}, Eric Verdin¹, Pedro Carrera-Bastos⁶, Sasha Targ^{4,7}, Claudio Franceschi^{8,9}, Luigi Ferrucci¹⁰, Derek W. Gilroy¹¹, Alessio Fasano¹², Gary W. Miller¹³, Andrew H. Miller¹⁴, Alberto Mantovani^{15,16,17}, Cornelia M. Weyand¹⁸, Nir Barzilai¹⁹, Jorg J. Goronzy²⁰, Thomas A. Rando^{20,21,22}, Rita B. Effros²³, Alejandro Lucia^{24,25}, Nicole Kleinsteuber^{26,27}, George M. Slavich²⁸

¹Buck Institute for Research on Aging, Novato, CA, USA.

²Stanford 1000 Immunomes Project, Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA, USA.

³Institute for Research in Translational Medicine, Universidad Austral, CONICET, Pilar, Buenos

Indeed, chronic inflammatory diseases have been recognized as the most significant cause of death in the world today,

⁷Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA, USA.

⁸IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy.

⁹Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia.

¹⁰Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA.

¹¹Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, UK.

¹²MassGeneral Hospital for Children, Harvard Medical School, Boston, MA, USA.

¹³Department of Environmental Health Sciences, School of Public Health, Columbia University Medical Center, New York, NY, USA.

Reprints and permissions information is available at www.nature.com/reprints.

*Correspondence should be addressed to D.F., furmand@stanford.edu.

Peer review information Hannah Stower was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



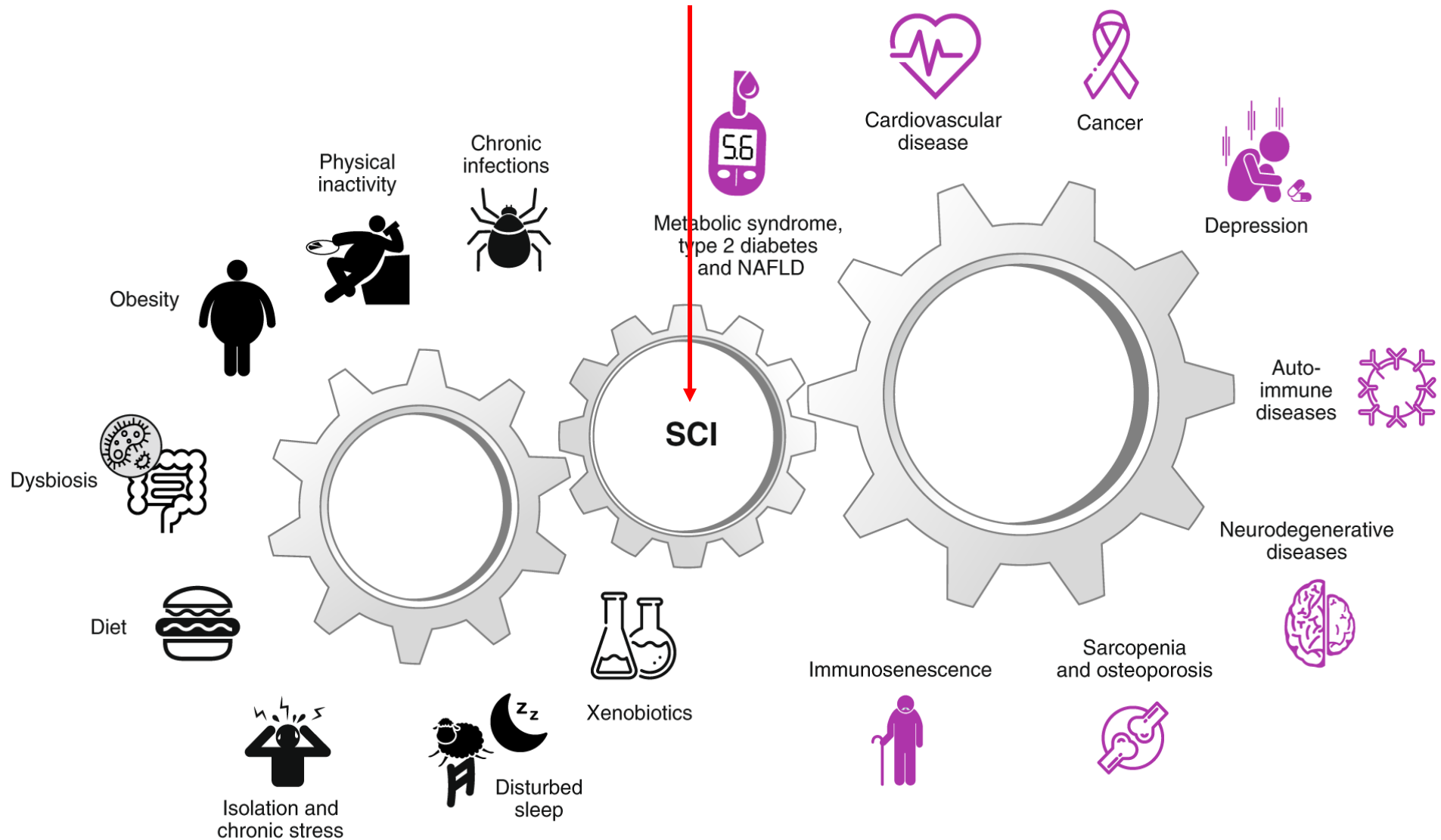
WE ARE UNDER ATTACK
FIGHT AND DEFEND

Premise #3

What is our Immune System Protecting Us From?



Systemic Chronic Inflammation





Published in final edited form as:

Nat Med. 2019 December ; 25(12): 1822–1832. doi:10.1038/s41591-019-0675-0.

Chronic inflammation in the etiology of disease across the life span

David Furman^{1,2,3,4,*}, Judith Campisi^{1,5}, Eric Verdin¹, Pedro Carrera-Bastos⁶, Sasha Targ^{4,7}, Claudio Franceschi^{8,9}, Luigi Ferrucci¹⁰, Derek W. Gilroy¹¹, Alessio Fasano¹², Gary W. Miller¹³, Andrew H. Miller¹⁴, Alberto Mantovani^{15,16,17}, Cornelia M. Weyand¹⁸, Nir Barzilai¹⁹, Jorg J. Goronzy²⁰, Thomas A. Rando^{20,21,22}, Rita B. Effros²³, Alejandro Lucia^{24,25}, Nicole Kleinsteuber^{26,27}, George M. Slavich²⁸

¹Buck Institute for Research on Aging, Novato, CA, USA.

²Stanford 1000 Immunomes Project, Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA, USA.

³Institute for Research in Translational Medicine, Universidad Austral, CONICET, Pilar, Buenos

Indeed, chronic inflammatory diseases have been recognized as the most significant cause of death in the world today,

⁷Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA, USA.

⁸IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy.

⁹Department of Applied Mathematics and Laboratory of Systems Biology of Aging, Lobachevsky University, Nizhny Novgorod, Russia.

¹⁰Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA.

¹¹Centre for Clinical Pharmacology and Therapeutics, Division of Medicine, University College London, London, UK.

¹²MassGeneral Hospital for Children, Harvard Medical School, Boston, MA, USA.

¹³Department of Environmental Health Sciences, School of Public Health, Columbia University Medical Center, New York, NY, USA.

Reprints and permissions information is available at www.nature.com/reprints.

*Correspondence should be addressed to D.F., furmand@stanford.edu.

Peer review information Hannah Stower was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript



Review

Immune Influencers in Action: Metabolites and Enzymes of the Tryptophan-Kynurenine Metabolic Pathway

Masaru Tanaka ^{1,2} , Fanni Tóth ¹, Helga Polyák ², Ágnes Szabó ², Yvette Mándi ³ and László Vécsei ^{1,2,*}

¹ MTA-SZTE—Neuroscience Research Group, H-6725 Szeged, Hungary;

tanaka.masaru.1@med.u-szeged.hu (M.T.); toth.fanni@med.u-szeged.hu (F.T.)

² Interdisciplinary Excellence Centre, Department of Neurology, Faculty of Medicine, University of Szeged, H-6725 Szeged, Hungary; polyak.helga@med.u-szeged.hu (H.P.); szabo.agnes.4@med.u-szeged.hu (A.S.)

³ Department of Medical Microbiology and Immunology, Faculty of Medicine, University of Szeged, H-6720 Szeged, Hungary; mandi.yvette@med.u-szeged.hu

* Correspondence: vecsei.laszlo@med.u-szeged.hu; Tel.: +36-62-545-351

Abstract: The tryptophan (TRP)-kynurenine (KYN) metabolic pathway is a main player of TRP metabolism through which more than 95% of TRP is catabolized. The pathway is activated by acute and chronic immune responses leading to a wide range of illnesses including cancer, immune

Chronic LGI is characterized by the long-term unresolved inflammatory condition in which proinflammatory and anti-inflammatory factors are continuously being released and fail to cease their actions

Academic Editor: Rosanna Di Paola

Received: 10 June 2021

Accepted: 23 June 2021

Published: 25 June 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

to explore the linkage between chronic LGI, KYNs, and major psychiatric disorders, including depressive disorder, bipolar disorder, substance use disorder, post-traumatic stress disorder, schizophrenia and autism spectrum disorder.

Keywords: chronic inflammation; low-grade inflammation; immune tolerance; inflammatory factor; kynurenine; kynurenic acid; depression; bipolar disorder; substance use disorder; post-traumatic stress disorder; schizophrenia; autism spectrum disorder

1. Introduction

Chronic low-grade inflammation (LGI) has been linked to the prodromal stage of a broad range of chronic illnesses such as cardiovascular-, metabolic-, immunologic-, neurodegenerative- and psychiatric diseases [1]. Chronic LGI is characterized by the long-term of unresolved inflammatory condition in which proinflammatory and anti-inflammatory factors are continuously released and fail to cease their actions (Figure 1a). The long-lasting release of the inflammatory factors initiates compensatory immune suppression and consequently causes immune tolerance, a condition in which the immune system is unresponsive to particular antigens that normally elicit an immune response (Figure 1b).



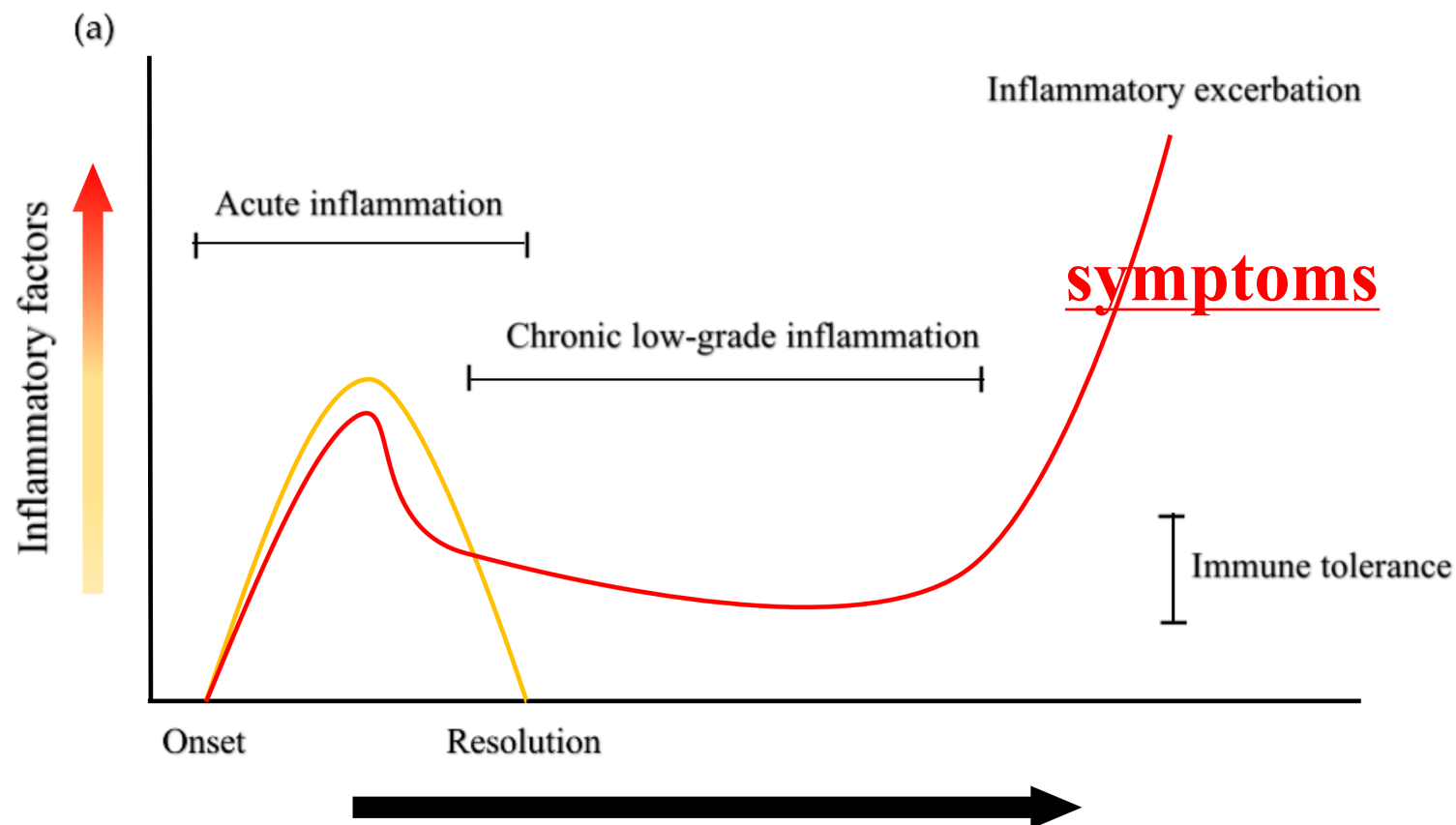


Figure 1. Acute inflammation, chronic low-grade inflammation and the status of pro-inflammatory and anti-inflammatory factors

Chronic low-grade inflammation (LGI) is characterized by a period of relatively low-level inflammatory factors that induce immune tolerance.

Eventually, (if the antigen exposure continues), inflammatory factors increase, leading to inflammatory exacerbation and contributing to the pathogenesis of various diseases (red line)



Anti-Inflammatory Potential of Probiotic Strain *Weissella cibaria* JW15 Isolated from Kimchi through Regulation of NF- κ B and MAPKs Pathways in LPS-Induced RAW 264.7 Cells

Hyung-Seok Yu¹, Na-Kyoung Lee¹, Ae-Jin Choi², Jeong-Sook Choe², Chun Ho Bae³, and Hyun-Dong Paik^{1*}

¹Department of Food Science and Biotechnology of Animal Resources, Konkuk University, Seoul 05029, Republic of Korea

²Functional Food and Nutrition Division, Department of Agrofood Resources, National Academy of Agricultural Science, Rural Development Administration, Jeollabuk-do 55365, Republic of Korea

³Aram Co., Ltd., Gyeonggi-do 12735, Republic of Korea

Received: March 7, 2019
Revised: June 18, 2019
Accepted: June 19, 2019

Probiotics are known to provide the host with immune-modulatory effects and are therefore of

The inflammatory response is a multi-cascade defensive process against external invasion, including elimination of stimuli and initiation of recovery processes, and is therefore crucial for maintaining health.

pISSN 1017-7825, eISSN 1738-8872

Copyright© 2019 by
The Korean Society for Microbiology
and Biotechnology

Keywords: *Weissella cibaria* JW15, kimchi, probiotics, anti-inflammation, nuclear factor- κ B, mitogen-activated protein kinase

Introduction

Inflammation is a basic host defense response against external invasions and is necessary for the restoration and maintenance of health [1]. Macrophages, a type of innate immune cell, predominantly mediate inflammatory responses through phagocytosis and release of pro-inflammatory molecules that include cytokines, such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α . [2]. The activation of macrophages is triggered by various stimuli including lipopolysaccharides (LPS), which are endotoxins originated from Gram-negative pathogens, and

results in the activation of inflammation-related cellular signaling pathways, such as the mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)- κ B [3]. The activation of MAPKs and NF- κ B up-regulates the expression of inflammatory genes and is followed by production of pro-inflammatory mediators including cytokines, nitric oxide (NO) and prostaglandin E₂ (PGE₂). However, prolonged or excessive expression of those inflammatory mediators may result in inflammatory disorders or cancer [4].

As the largest portion of the microbiome is the gastrointestinal tract (GIT), the intestinal microbiota of the host is the primary source of microbe-derived beneficial

Review

Undigested Food and Gut Microbiota May Cooperate in the Pathogenesis of Neuroinflammatory Diseases: A Matter of Barriers and a Proposal on the Origin of Organ Specificity

Paolo Riccio and Rocco Rossano *

Department of Sciences, University of Basilicata, 85100 Potenza, Italy; paoloxriccio@gmail.com

* Correspondence: rocco.rossano@unibas.it

Received: 1 October 2019; Accepted: 8 November 2019; Published: 9 November 2019



Abstract: As food is an active subject and may have anti-inflammatory or pro-inflammatory effects, dietary habits may modulate the low-grade neuroinflammation associated with chronic neurodegenerative diseases. Food is living matter different from us, but made of our own nature. Therefore, it is at the same time foreign to us (*non-self*), if not yet digested, and like us (*self*), after its complete digestion. To avoid the efflux of undigested food from the lumen, the intestinal barrier

If the cause of inflammation persists, the inflammation also persists, usually with low intensity, and is called low-grade chronic inflammation.

Keywords: diet; gut microbiota; inflammation; intestinal barrier; blood-brain barrier; Alzheimer's disease; Parkinson's disease; multiple sclerosis; autism spectrum disorders; amyotrophic lateral sclerosis

1. Chronic Neurodegenerative Diseases are Associated with Low-Grade Chronic Inflammation

Despite having different etiology and different pathogenic mechanisms, chronic neurodegenerative diseases, such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and autism spectrum disorder (ASD), all have an inflammatory nature in common [1] (Figure 1).

Fighting the inflammatory processes that underlie these diseases may reduce their progression and their severity. Inflammation is an innate, non-specific defense process [2,3]. It occurs in response to the presence of foreign material (*non-self*), or as a consequence of tissue damage caused by physical, chemical or biological agents, or by abnormalities such as the failure to eliminate waste or digest nutrients. If the cause of inflammation persists, the inflammation also persists, usually with low intensity, and is called low-grade chronic inflammation. As for the chronic neuroinflammatory diseases, in most cases, the neuroinflammatory state does not originate in the central nervous system (CNS), but is thought to come from a chronic systemic inflammation (CSI) [4–6]. Recent evidence suggests that CSI may in turn result from a persistent intestinal inflammation spreading through the intestinal

THE INFLAMMATION EQUATION

Decoding the Steps for Optimal Well-Being



Enter your details below to save your seat!

First Name *

Email *

Are you a healthcare provider? *

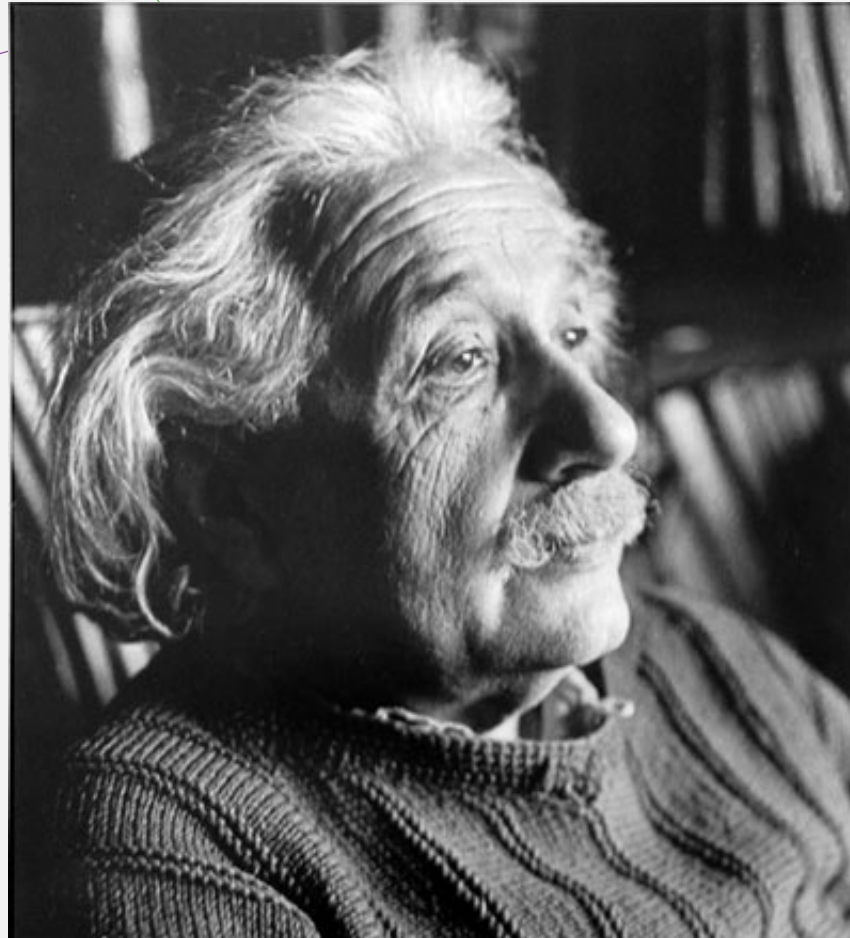
- ☐ Yes
- ☐ No

I'M READY TO TAME THE FLAME

Your information is secure and handled in accordance of our [privacy policy](#).



***“Everything should be made as simple as possible,
but not simpler”***



Premise #4

How many come to HEALCON with the basic platform belief, the more fruit and vegetables in the diet, the better?



A global deficiency of nutrition education in physician training: the low hanging fruit in medicine remains on the vine



According to the 2019 Global Burden of Disease Study of 195 countries,¹ dietary factors are the single leading cause of death, exacting an even greater health burden than smoking. For that reason, if medical education were to be based solely on the needs of patient and population health, nutrition would surely be meaningfully addressed.

But, in defiance of the obvious need for physicians to possess, at minimum, solid foundational skills in clinical nutrition, medical education in nutrition across the globe is decidedly lacking. That is the conclusion of the study by Jennifer Crowley and colleagues in

be similar on every continent studied—a perceived lack of interest and expertise among faculty members in nutrition, low-quality nutrition curriculum that did not appear to be prioritised, and few examples of nutritional counselling during clinical years to serve as models for emerging physicians.

Each geographic region has a unique set of predominant nutritional challenges and opportunities, nevertheless, a global need exists for physicians to understand the strong connection between nutrition and health. For example, in the past 30 years, the global

See [Articles](#) page e379

According to the 2019 Global Burden of Disease Study of 195 countries, dietary factors are the single leading cause of death, exacting an even greater health burden than smoking.

similar. Nutrition knowledge and confidence in counselling among medical students were uniformly low, as was the students' perception of both the quality and quantity of their nutrition education.

Despite the paucity of nutrition curriculum in medical school, the study found that interest among medical students in nutrition is uniformly high. Previous research has shown that keen interest in nutrition among incoming medical students typically wanes by the time of graduation.³ It is easy to imagine why. When medical students do not see nutrition substantively incorporated into their curriculum and do not observe clinical mentors incorporating nutritional interventions into their care plans, what else can they conclude but that nutrition is not as important as they had once believed?

The review by Crowley and colleagues² adds to the existing medical literature⁴ in framing the gap in nutrition education in medical school as a global phenomenon as well as providing a glimpse of a blueprint for moving forward.

The obstacles to delivering meaningful nutrition education are well described in this study and appear to

nutrition, now can they take a meaningful role in aiding this dietary shift toward a plant sourced diet so necessary for both personal and planetary health?

There is no question that dietary intake, both on an individual and population basis, is a function of a great many inputs including food access, economics, cultural traditions, marketing, and more. Nevertheless, patients generally rely on their physicians for guidance and there is ample evidence that physician discussions of diet make a positive impact on patient dietary choices.⁷ As aptly described in the review by Crowley and colleagues "a poorly trained medical workforce can be viewed in and of itself as one structural contributor to diet-related disease."²

Also noted in the study, nutritional interventions in medicine are best considered a team effort delivered by a group of health professionals skilled in nutritional care. But without a solid foundation of clinical nutrition knowledge and skills, physicians worldwide are generally not equipped to even begin to have an informed nutrition conversation with their patients and to fully identify opportunities for referral.



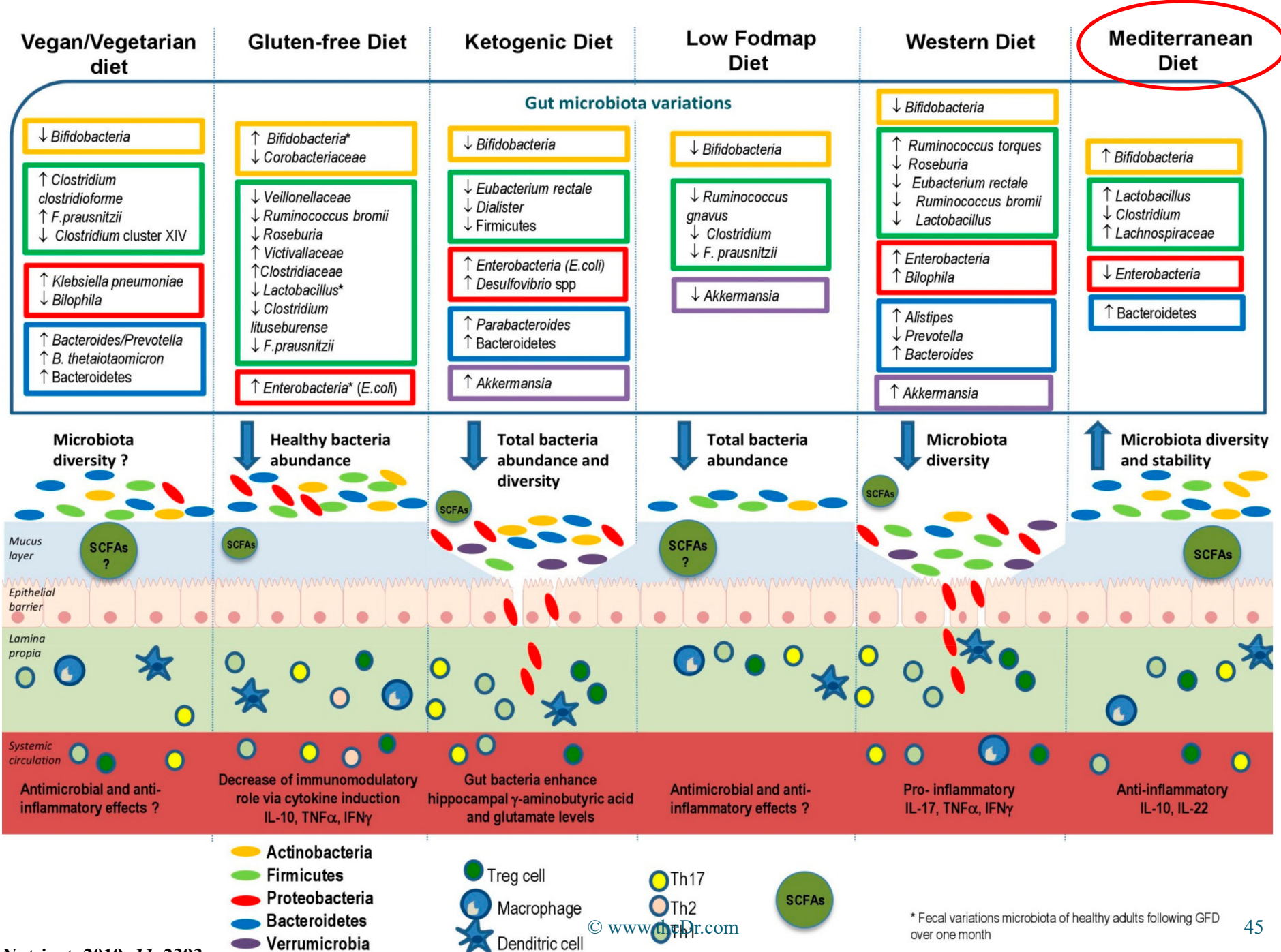
Yes, we all live with the foundational paradigm of the necessity of focusing on fruits and vegetables in our food selection plans, but are we open to current science? Are we willing to adjust our paradigm, our belief system taking into consideration undeniable facts?

*Are you willing to adjust
your belief system?*



Mediterranean Diet







Original Investigation | Nutrition, Obesity, and Exercise

Association of a Mediterranean Diet Pattern With Adverse Pregnancy Outcomes Among US Women

Nour Makarem, PhD, MS; Kristi Chau, MA; Eliza C. Miller, MD, MS; Cynthia Gyamfi-Bannerman, MD, MS; Isabella Tous, BS; Whitney Booker, MD; Janet M. Catov, PhD, MS; David M. Haas, MD, MS; William A. Grobman, MD, MBA; Lisa D. Levine, MD, MSCE; Rebecca McNeil, PhD; C. Noel Bairey Merz, MD; Uma Reddy, MD, MPH; Ronald J. Wapner, MD; Melissa S. Wong, MD, MHDS; Natalie A. Bello, MD, MPH

Abstract

IMPORTANCE The Mediterranean diet pattern is inversely associated with the leading causes of morbidity and mortality, including metabolic diseases and cardiovascular disease, but there are limited data on its association with adverse pregnancy outcomes (APOs) among US women.

OBJECTIVE To evaluate whether concordance to a Mediterranean diet pattern around the time of conception is associated with lower risk of developing any APO and individual APOs.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter, cohort study, the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be, enrolled 10 038 women between October 1, 2010, and September 30, 2013, with a final analytic sample of 7798 racially

Key Points

Question Among geographically, racially, and ethnically diverse nulliparous US women, is concordance to a Mediterranean diet around the time of conception associated with risk of developing any adverse pregnancy outcome (APO) and individual APOs?

Findings In this cohort study of 7798 women, greater concordance to a Mediterranean diet pattern was

Greater adherence to a Mediterranean diet pattern has been associated with a lower risk for multiple chronic diseases and mortality.

stillbirth.

RESULTS Of 7798 participants (mean [SD] age, 27.4 [5.5] years), 754 (9.7%) were aged 35 years or older, 816 (10.5%) were non-Hispanic Black, 1294 (16.6%) were Hispanic, and 1522 (19.5%) had obesity at baseline. The mean (SD) aMed score was 4.3 (2.1), and the prevalence of high, moderate, and low concordance to a Mediterranean diet pattern around the time of conception was 30.6% (n=2388), 31.2% (n=2430), and 38.2% (n=2980), respectively. In multivariable models, a high vs low aMed score was associated with 21% lower odds of any APO (adjusted odds ratio [aOR], 0.79 [95% CI, 0.68-0.92]), 28% lower odds of preeclampsia or eclampsia (aOR, 0.72 [95% CI, 0.55-0.93]), and 37% lower odds of gestational diabetes (aOR, 0.63 [95% CI, 0.44-0.90]). There were no differences by race, ethnicity, and prepregnancy body mass index, but associations were stronger among women aged 35 years or older (aOR, 0.54 [95% CI, 0.34-0.84]; $P = .02$ for interaction). When aMed score quintiles were evaluated, similar associations were observed, with higher scores being inversely associated with the incidence of any APO.

CONCLUSIONS AND RELEVANCE This cohort study suggests that greater adherence to a Mediterranean diet pattern is associated with lower risk of APOs, with evidence of a dose-response

studies are needed to assess whether promoting a Mediterranean-style diet around the time of conception and throughout pregnancy can prevent APOs.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

(continued)

Open Access. This is an open access article distributed under the terms of the CC-BY License.

JAMA Network Open. 2022;5(12):e2248165. doi:10.1001/jamanetworkopen.2022.48165

December 22, 2022 1/13



**But What About in
the Vulnerable?**





Original Investigation | Nutrition, Obesity, and Exercise

Association of a Mediterranean Diet Pattern With Adverse Pregnancy Outcomes Among US Women

Nour Makarem, PhD, MS; Kristi Chau, MA; Eliza C. Miller, MD, MS; Cynthia Gyamfi-Bannerman, MD, MS; Isabella Tous, BS; Whitney Booker, MD; Janet M. Catov, PhD, MS; David M. Haas, MD, MS; William A. Grobman, MD, MBA; Lisa D. Levine, MD, MSCE; Rebecca McNeil, PhD; C. Noel Bairey Merz, MD; Uma Reddy, MD, MPH; Ronald J. Wapner, MD; Melissa S. Wong, MD, MHDS; Natalie A. Bello, MD, MPH

Abstract

IMPORTANCE The Mediterranean diet pattern is inversely associated with the leading causes of morbidity and mortality, including metabolic diseases and cardiovascular disease, but there are

Key Points

Question Among geographically, racially, and ethnically diverse nulliparous US women, is adherence

The primary outcome was the development of any APO, defined as developing 1 or more of the following: gestational hypertension, preeclampsia or eclampsia, gestational diabetes, preterm birth (medically indicated or spontaneous live birth at <37 weeks' gestational age, delivery of a small-for-gestational-age infant (<5th percentile by Alexander nomogram), or stillbirth

(n=2388), 31.2% (n=2430), and 38.2% (n=2980), respectively. In multivariable models, a high vs low aMed score was associated with 21% lower odds of any APO (adjusted odds ratio [aOR], 0.79 [95% CI, 0.68-0.92]), 28% lower odds of preeclampsia or eclampsia (aOR, 0.72 [95% CI, 0.55-0.93]), and 37% lower odds of gestational diabetes (aOR, 0.63 [95% CI, 0.44-0.90]). There were no differences by race, ethnicity, and prepregnancy body mass index, but associations were stronger among women aged 35 years or older (aOR, 0.54 [95% CI, 0.34-0.84]; $P = .02$ for interaction). When aMed score quintiles were evaluated, similar associations were observed, with higher scores being inversely associated with the incidence of any APO.

CONCLUSIONS AND RELEVANCE This cohort study suggests that greater adherence to a Mediterranean diet pattern is associated with lower risk of APOs, with evidence of a dose-response

(continued)

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY License.

JAMA Network Open. 2022;5(12):e2248165. doi:10.1001/jamanetworkopen.2022.48165

December 22, 2022 1/13





Original Investigation | Nutrition, Obesity, and Exercise

Association of a Mediterranean Diet Pattern With Adverse Pregnancy Outcomes Among US Women

Nour Makarem, PhD, MS; Kristi Chau, MA; Eliza C. Miller, MD, MS; Cynthia Gyamfi-Bannerman, MD, MS; Isabella Tous, BS; Whitney Booker, MD; Janet M. Catov, PhD, MS; David M. Haas, MD, MS; William A. Grobman, MD, MBA; Lisa D. Levine, MD, MSCE; Rebecca McNeil, PhD; C. Noel Bairey Merz, MD; Uma Reddy, MD, MPH; Ronald J. Wapner, MD; Melissa S. Wong, MD, MHDS; Natalie A. Bello, MD, MPH

Abstract

IMPORTANCE The Mediterranean diet pattern is inversely associated with the leading causes of morbidity and mortality, including metabolic diseases and cardiovascular disease, but there are limited data on its association with adverse pregnancy outcomes (APOs) among US women.

OBJECTIVE To evaluate whether concordance to a Mediterranean diet pattern around the time of conception is associated with lower risk of developing any APO and individual APOs.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter, cohort study, the

Key Points

Question Among geographically, racially, and ethnically diverse nulliparous US women, is concordance to a Mediterranean diet around the time of conception associated with risk of developing any adverse pregnancy outcome (APO) and individual APOs?

Findings In this cohort study of 7798

The aMed score consists of 9 components: vegetables (excluding potatoes), fruits, nuts, whole grains, legumes, fish, monounsaturated to saturated fat ratio, red and processed meats, and alcohol.

RESULTS Of 7798 participants (mean [SD] age, 27.4 [5.5] years), 754 (9.7%) were aged 35 years or older, 816 (10.5%) were non-Hispanic Black, 1294 (16.6%) were Hispanic, and 1522 (19.5%) had obesity at baseline. The mean (SD) aMed score was 4.3 (2.1), and the prevalence of high, moderate, and low concordance to a Mediterranean diet pattern around the time of conception was 30.6% (n=2388), 31.2% (n=2430), and 38.2% (n=2980), respectively. In multivariable models, a high vs low aMed score was associated with 21% lower odds of any APO (adjusted odds ratio [aOR], 0.79 [95% CI, 0.68-0.92]), 28% lower odds of preeclampsia or eclampsia (aOR, 0.72 [95% CI, 0.55-0.93]), and 37% lower odds of gestational diabetes (aOR, 0.63 [95% CI, 0.44-0.90]). There were no differences by race, ethnicity, and prepregnancy body mass index, but associations were stronger among women aged 35 years or older (aOR, 0.54 [95% CI, 0.34-0.84]; $P = .02$ for interaction). When aMed score quintiles were evaluated, similar associations were observed, with higher scores being inversely associated with the incidence of any APO.

CONCLUSIONS AND RELEVANCE This cohort study suggests that greater adherence to a Mediterranean diet pattern is associated with lower risk of APOs, with evidence of a dose-response

(continued)

promoting a Mediterranean-style diet around the time of conception and throughout pregnancy can prevent APOs.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY License.

JAMA Network Open. 2022;5(12):e2248165. doi:10.1001/jamanetworkopen.2022.48165

December 22, 2022 1/13





Original Investigation | Nutrition, Obesity, and Exercise

Association of a Mediterranean Diet Pattern With Adverse Pregnancy Outcomes Among US Women

Nour Makarem, PhD, MS; Kristi Chau, MA; Eliza C. Miller, MD, MS; Cynthia Gyamfi-Bannerman, MD, MS; Isabella Tous, BS; Whitney Booker, MD; Janet M. Catov, PhD, MS; David M. Haas, MD, MS; William A. Grobman, MD, MBA; Lisa D. Levine, MD, MSCE; Rebecca McNeil, PhD; C. Noel Bairey Merz, MD; Uma Reddy, MD, MPH; Ronald J. Wapner, MD; Melissa S. Wong, MD, MHS; Natalie A. Bello, MD, MPH

Abstract

IMPORTANCE The Mediterranean diet pattern is inversely associated with the leading causes of morbidity and mortality, including metabolic diseases and cardiovascular disease, but there are limited data on its association with adverse pregnancy outcomes (APOs) among US women.

OBJECTIVE To evaluate whether concordance to a Mediterranean diet pattern around the time of conception is associated with lower risk of developing any APO and individual APOs.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter, cohort study, the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be, enrolled 10 038 women between October 1, 2010, and September 30, 2013, with a final analytic sample of 7798 racially, ethnically, and geographically diverse women with singleton pregnancies who had complete diet

Key Points

Question Among geographically, racially, and ethnically diverse nulliparous US women, is concordance to a Mediterranean diet around the time of conception associated with risk of developing any adverse pregnancy outcome (APO) and individual APOs?

Findings In this cohort study of 7798 women, greater concordance to a Mediterranean diet pattern was significantly associated with 21% lower

Of 7798 participants, a high vs low aMed score was associated with 21% lower odds of any APO

and defined as developing 1 or more of the following: preeclampsia or eclampsia, gestational hypertension, gestational diabetes, preterm birth, delivery of a small-for-gestational-age infant, or stillbirth.

RESULTS Of 7798 participants (mean [SD] age, 27.4 [5.5] years), 754 (9.7%) were aged 35 years or older, 816 (10.5%) were non-Hispanic Black, 1294 (16.6%) were Hispanic, and 1522 (19.5%) had obesity at baseline. The mean (SD) aMed score was 4.3 (2.1), and the prevalence of high, moderate, and low concordance to a Mediterranean diet pattern around the time of conception was 30.6% (n=2388), 31.2% (n=2430), and 38.2% (n=2980), respectively. In multivariable models, a high vs low aMed score was associated with 21% lower odds of any APO (adjusted odds ratio [aOR], 0.79 [95% CI, 0.68-0.92]), 28% lower odds of preeclampsia or eclampsia (aOR, 0.72 [95% CI, 0.55-0.93]), and 37% lower odds of gestational diabetes (aOR, 0.63 [95% CI, 0.44-0.90]). There were no differences by race, ethnicity, and prepregnancy body mass index, but associations were stronger among women aged 35 years or older (aOR, 0.54 [95% CI, 0.34-0.84]; $P = .02$ for interaction). When aMed score quintiles were evaluated, similar associations were observed, with higher scores being inversely associated with the incidence of any APO.

CONCLUSIONS AND RELEVANCE This cohort study suggests that greater adherence to a Mediterranean diet pattern is associated with lower risk of APOs, with evidence of a dose-response

Mediterranean diet pattern is inversely associated with APOs; intervention studies are needed to assess whether promoting a Mediterranean-style diet around the time of conception and throughout pregnancy can prevent APOs.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

(continued)

Open Access. This is an open access article distributed under the terms of the CC-BY License.

JAMA Network Open. 2022;5(12):e2248165. doi:10.1001/jamanetworkopen.2022.48165

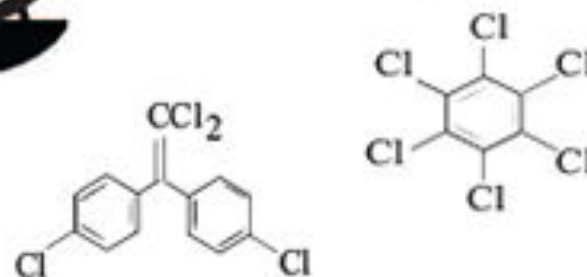
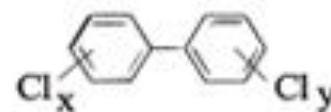
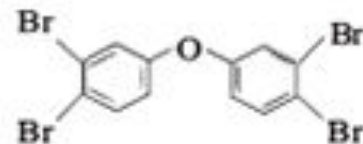
December 22, 2022 1/31

© www.theDr.com



**But What About in
the Most Vulnerable?**





Review article

The chemical erosion of human health: adverse environmental exposure and *in-utero* pollution – determinants of congenital disorders and chronic disease

The first 38 weeks of human life spent in the allegedly protected environment of the amniotic sac are medically more eventful and more fraught with danger than the next 38 years in the lifespan of most human individuals.

Dr. Ian Donald

Stephen J. Genuis*

Department of Obstetrics and Gynecology, Faculty of

cautionary avoidance; preconception care; prenatal care; toxicology.

The first 38 weeks of human life spent in the allegedly protected environment of the amniotic sac are medically more eventful and more fraught with danger than the next 38 years in the lifespan of most human individuals

health problems including various congenital anomalies. As a result of increasing concern about environmental influences on health, 'Human Exposure Assessment,' the investigation and study of specific patient exposures and related health concerns, is a rapidly expanding area of scientific research. Practitioners of clinical medicine, including providers of maternity care, should acquire the skills to elicit a proper environmental exposure history and the necessary tools to implement proactive patient education relating to precautionary avoidance.

Keywords: Chronic disease; congenital anomalies; endocrine disrupting chemicals; environmental health; hormone disruption; human exposure assessment; pre-

delivered healthy offspring [144], raises intrigue about the underlying etiology of various congenital disorders. When the author reviewed the medical literature in pursuit for an explanation, it became apparent that environmental and toxicological factors are significant determinants of many contemporary health issues, including birth deformities. As few medical schools include courses about environmental medicine in their curricula [50], awareness of toxicants as ubiquitous determinants of impaired health is often lacking among physicians and few practitioners have acquired the necessary skills to investigate and manage exposure-related illness [89].

Trends in chronic illness

Although life expectancy has improved over the last century in developed nations in large measure due to the immense progress at reducing infant mortality, the expanding prevalence of chronic and degenerative illness

*Corresponding author:
Dr. Stephen Genuis, MD
FRCSC, DABOG, 2935-66 Street
Edmonton, Alberta
Canada T6K 4C1
Tel.: +1 (780) 450 3504
Fax: +1 (780) 490 1803
E-mail: sgenuis@ualberta.ca



REPRODUCTIVE ENDOCRINOLOGY

Exposure to pesticide residues linked to adverse pregnancy outcomes

In the field of endocrinology, there is interest in examining the health effects of exposure to pesticide residues in the general population. Mouse studies have shown that early exposure to very low doses of pesticides during pregnancy can

In their study, Jorge Chavarro and colleagues examined whether exposure to environmentally relevant concentrations of pesticide residues, through contamination from fruits and vegetables, is related to pregnancy outcomes in women of

who consumed <1 serving per day. Chavarro explains that most of the observed difference resulted from an increase in pregnancy losses happening very early in pregnancy, which is consistent with mouse models.

“...new research suggests that the ingestion

New research suggests that the ingestion of pesticide-treated fruits and vegetables is associated with a reduced chance of pregnancy and an increased chance of pregnancy loss in humans.



exposure to pesticides and that most of this exposure is from consumption of fruits and vegetables.”

The investigators report that women who ingest ≥ 2.3 servings per day of highly contaminated fruits and vegetables were less likely to become pregnant or to have a live birth as a result of assisted reproductive technology than women

organic version of high-pesticide residue produce, is not a bad idea.”

Alan Morris

ORIGINAL ARTICLE Chiu, Y.-H. et al. Association between pesticide residue intake from consumption of fruits and vegetables and pregnancy outcomes among women undergoing infertility treatment with assisted reproductive technology. *JAMA Intern. Med.* <http://dx.doi.org/10.1001/jamainternmed.2017.5018> (2017)



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS This analysis included 325 women who completed a

Invited Commentary page 26

Supplemental content

“an elegant example of a prospective epidemiological study that uses sophisticated biological markers to identify a subclinical effect of pesticide exposure on human health”

servings/d, respectively. Greater intake of high-pesticide residue FVs was associated with a lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (≥ 2.3 servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes

A range of potentially confounding factors was considered, and none changed the study outcome.

- age (years),
- BMI,
- smoking status (current/former vs never),
- race (white vs nonwhite),
- supplemental folate intake (micrograms per day),
- residential pesticide exposure history (yes vs no),
- prudent and Western dietary patterns,
- total energy intake (kilocalories per day), and
- infertility diagnosis (male factor vs female factor vs unexplained).



JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Conflicts of Interest: None reported.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).

Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

Invited Commentary page 26

Supplemental content

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS This analysis included 325 women who completed a

To the best of our knowledge, this is the first prospective study evaluating the relationship of dietary pesticide exposure to reproductive success in humans.

servings/d, respectively. Greater intake of high-pesticide residue FVs was associated with a lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (≥ 2.3 servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits

[Invited Commentary page 26](#)

[Supplemental content](#)

Compared with women in the lowest quartile of high-pesticide fruit and vegetable intake (<1.0 servings/d), women in the highest quartile (2.3 servings/d) had:

- **18% lower probability of clinical pregnancy and**
- **26% lower probability of live birth.**

servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

Invited Commentary page 26

High-pesticide residue FV intake was positively associated with probability of total pregnancy loss. The adjusted probabilities of total pregnancy loss were:

- 7% (95% CI, 3%-15%),
- 23% (95% CI, 16%-33%),
- 24% (95% CI, 15%-36%), and
- 34% (95% CI, 20%-51%)

for women in increasing quartiles of high-pesticide residue FV intake



JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS This analysis included 325 women who completed a

Invited Commentary page 26

Supplemental content

Greater intake of high–pesticide residue Fruits and Vegetables was associated with a lower probability of clinical pregnancy and live birth.

servings/d, respectively. Greater intake of high-pesticide residue FVs was associated with a lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (≥ 2.3 servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

Invited Commentary page 26

Supplemental content

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS This analysis included 325 women who completed a diet assessment and subsequently underwent 541 ART cycles in the Environment and Reproductive Health (EARTH) prospective cohort study (2007-2016) at a fertility center at

Low-pesticide residue FV intake was inversely associated with early pregnancy loss

RESULTS In the 325 participants (mean [SD] age, 35.1 [4.0] y; body mass index, 24.1 [4.3]), mean (SD) intakes of high- and low-pesticide residue FVs were 1.7 (1.0) and 2.8 (1.6) servings/d, respectively. Greater intake of high-pesticide residue FVs was associated with a lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (≥ 2.3 servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

Invited Commentary page 26

Supplemental content

We considered women to be organic FV consumers if they consumed organic FVs at least 3 times per week. Women with lower intake of organic FVs (<3 times/wk) were considered to be conventional FV consumers.

lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (≥ 2.3 servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS This analysis included 325 women who completed a

[Invited Commentary page 26](#)

[Supplemental content](#)

Regular consumption of conventionally grown, pesticide-treated fruits and vegetables was associated with increased risk of pregnancy loss, while consumption of organic fruits and vegetables significantly reduced risk of pregnancy loss and increased fertility.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS This analysis included 325 women who completed a diet assessment and subsequently underwent 541 ART cycles in the Environment and Reproductive Health (EARTH) preconception cohort study (2007-2016) at fertility centers in

← Invited Commentary page 26

+ Supplemental content

All dietary pesticide levels were within the range of typical American exposure.

RESULTS In the 325 participants (mean [SD] age, 35.1 [4.0] y; body mass index, 24.1 [4.3]), mean (SD) intakes of high- and low-pesticide residue FVs were 1.7 (1.0) and 2.8 (1.6) servings/d, respectively. Greater intake of high-pesticide residue FVs was associated with a lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (<1.0 servings/d), women in the highest quartile (≥ 2.3 servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.



JAMA Internal Medicine | Original Investigation

Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Han Chiu, MD, ScD; Paige L. Williams, PhD; Matthew W. Gillman, MD, SM; Audrey J. Gaskins, ScD; Lidia Mínguez-Alarcón, PhD; Irene Souter, MD; Thomas L. Toth, MD; Jennifer B. Ford, RN; Russ Hauser, MD, ScD; Jorge E. Chavarro, MD, ScD; for the EARTH Study Team

[Invited Commentary page 26](#)

[Supplemental content](#)

IMPORTANCE Animal experiments suggest that ingestion of pesticide mixtures at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE To examine the association of preconception intake of pesticide residues in fruits

servings/d) had 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE Higher consumption of high-pesticide residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

JAMA Intern Med. 2018;178(1):17-26. doi:10.1001/jamainternmed.2017.5038
Published online October 30, 2017.

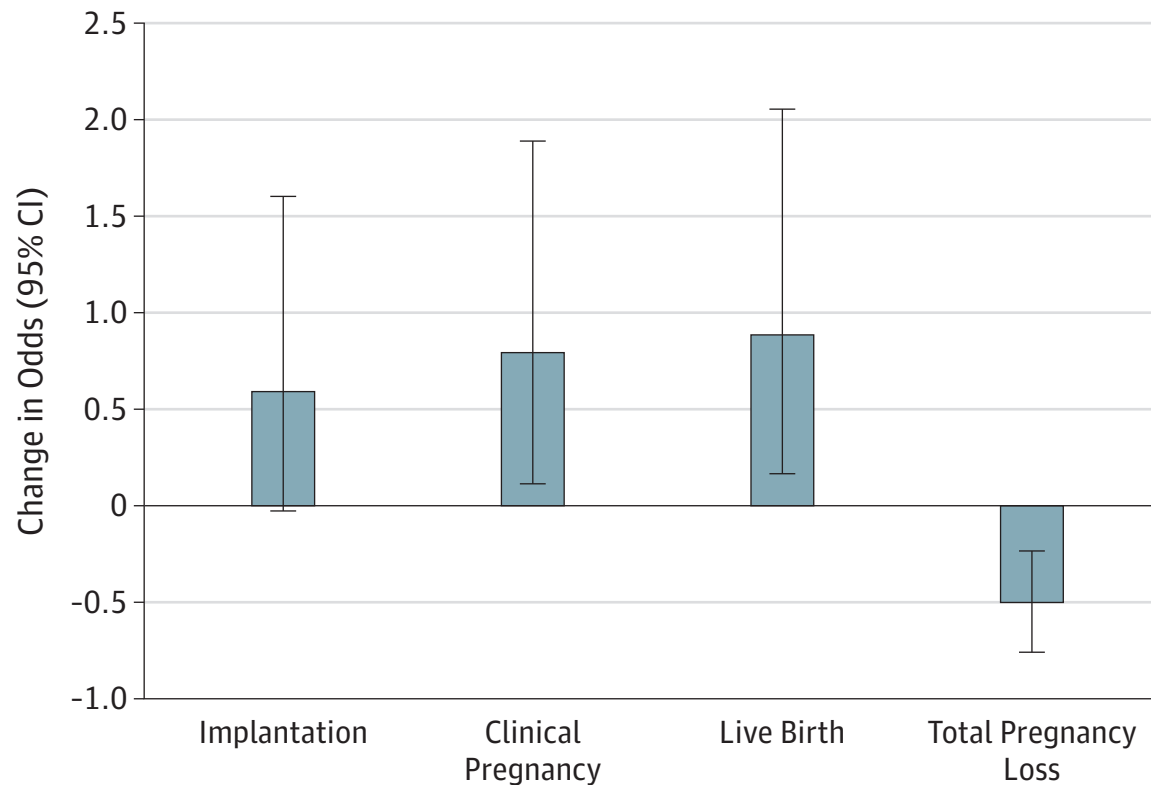
Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EARTH Study Team members are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, 665 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).



Figure 2. Estimated Changes in Odds Ratios of Clinical Outcomes by Replacing 1 Serving/d of High-Pesticide Residue Fruits and Vegetables With 1 Serving/d of Low-Pesticide Residue Fruits and Vegetables



Data were adjusted for age, body mass index, smoking status, race, folate supplementation, organic fruit and vegetable consumption frequency, residential pesticide exposure history, total energy intake, Western and prudent pattern scores, and infertility diagnosis. Error bars indicate 95% confidence interval.



REPRODUCTIVE ENDOCRINOLOGY

Exposure to pesticide residues linked to adverse pregnancy outcomes

In the field of endocrinology, there is interest in examining the health effects of exposure to pesticide residues in the general population. Mouse studies have shown that

In their study, Jorge Chavarro and colleagues examined whether exposure to environmentally relevant concentrations of pesticide residues, through contamination

who consumed <1 serving per day. Chavarro explains that most of the observed difference resulted from an increase in pregnancy losses happening very early in



...new research suggests that

The investigators report that women who ingest ≥ 2.3 servings per day of highly contaminated fruits and vegetables were less likely to become pregnant or to have a live birth as a result of assisted reproductive technology than women who consumed <1 serving per day.

Jessie Valle/Macmillan Publishers



of fruits and vegetables."

The investigators report that women who ingest ≥ 2.3 servings per day of highly contaminated fruits and vegetables were less likely to become pregnant or to have a live birth as a result of assisted reproductive technology than women

Alan Morris

ORIGINAL ARTICLE Chiu, Y.-H. et al. Association between pesticide residue intake from consumption of fruits and vegetables and pregnancy outcomes among women undergoing infertility treatment with assisted reproductive technology. *JAMA Intern. Med.* <http://dx.doi.org/10.1001/jamainternmed.2017.5018> (2017)

REPRODUCTIVE ENDOCRINOLOGY

Exposure to pesticide residues linked to adverse pregnancy outcomes

In the field of endocrinology, there is interest in examining the health effects of exposure to pesticide residues in the general population. Mouse studies have shown that early exposure to very low doses of pesticides during pregnancy can lead to cell death in embryos, but whether the same is true for humans

In their study, Jorge Chavarro and colleagues examined whether exposure to environmentally relevant concentrations of pesticide residues, through contamination from fruits and vegetables, is related to pregnancy outcomes in women of reproductive age who were attending a fertility clinic. The amount of

who consumed <1 serving per day. Chavarro explains that most of the observed difference resulted from an increase in pregnancy losses happening very early in pregnancy, which is consistent with mouse models.

"To move this forward we need to improve how we assess



...new research suggests that the ingestion of pesticide-treated fruits

Most of the observed difference resulted from an increase in pregnancy losses happening very early in pregnancy, which is consistent with mouse models.

Jessie Vella/Macmillan Publishers Limited



grown produce to eating organic produce can substantially decrease exposure to pesticides and that most of this exposure is from consumption of fruits and vegetables."

The investigators report that women who ingest ≥ 2.3 servings per day of highly contaminated fruits and vegetables were less likely to become pregnant or to have a live birth as a result of assisted reproductive technology than women

produce, by either consuming low-pesticide residue produce or the organic version of high-pesticide residue produce, is not a bad idea."

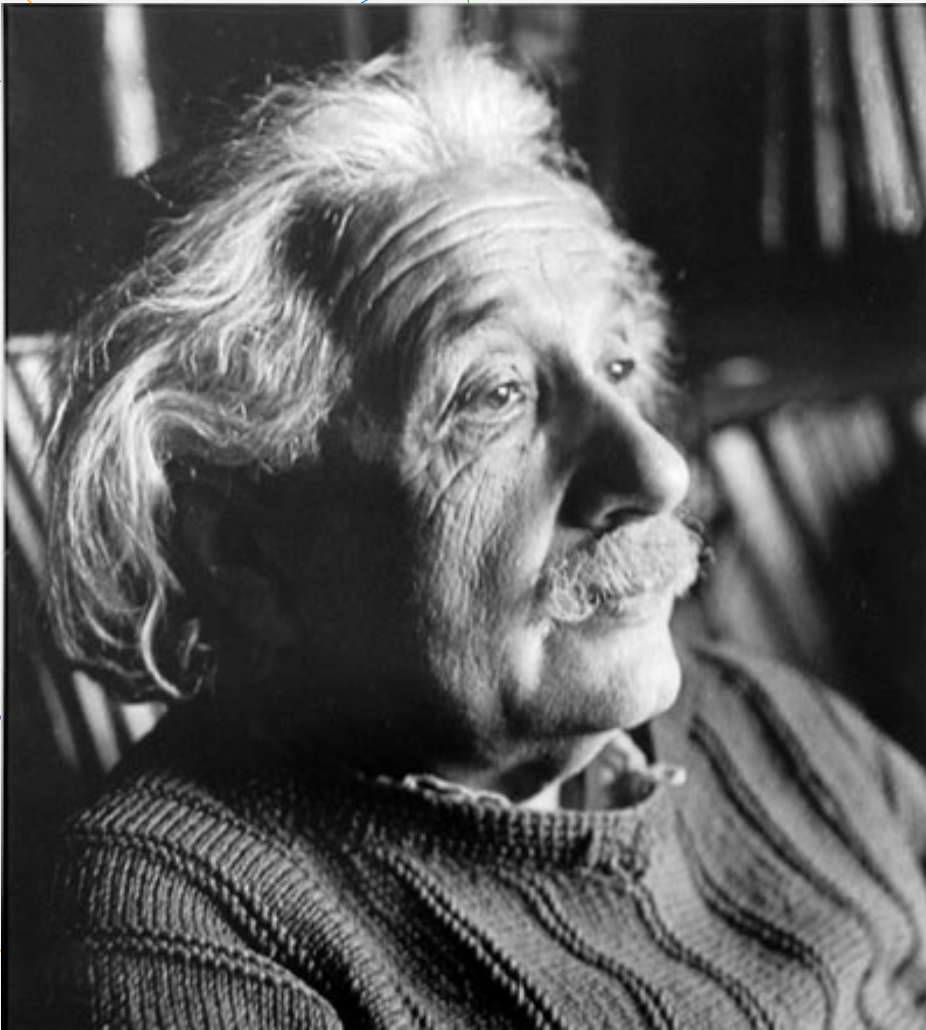
Alan Morris

ORIGINAL ARTICLE Chiu, Y.-H. et al. Association between pesticide residue intake from consumption of fruits and vegetables and pregnancy outcomes among women undergoing infertility treatment with assisted reproductive technology. *JAMA Intern. Med.* <http://dx.doi.org/10.1001/jamainternmed.2017.5018> (2017)



With a 4-9% increase in every autoimmune disease, every year, can you see the value in going back to 'The Prime Directive', and reduce the triggers of inflammation in every patient?





Time For a Paradigm Shift



So What Do We Recommend Regarding the Mediterranean Diet?



Premise #5

When it is not possible to Eat Organic all the Time, What Do You Do?



DIRTY DOZEN™

EWG's 2023 Shopper's Guide to Pesticides in Produce™



1. Strawberries



2. Spinach



3. Kale, collard &
mustard greens



4. Peaches



5. Pears



6. Nectarines



7. Apples



8. Grapes



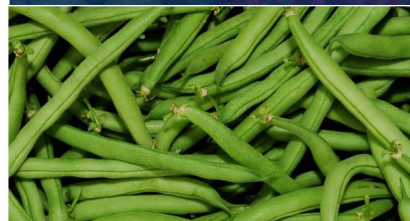
9. Bell & hot Peppers



10. Cherries



11. Blueberries



12. Green Beans



CLEAN FIFTEEN™

EWG's 2023 Shopper's Guide to Pesticides in Produce™



1. Avocados



2. Sweet corn*



3. Pineapple



4. Onions



5. Papaya*



6. Sweet peas (frozen)



7. Asparagus



8. Honeydew melon



9. Kiwi



10. Cabbage



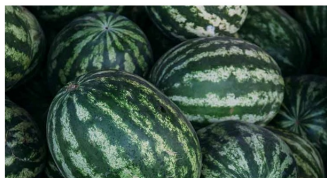
11. Mushrooms



12. Mangoes



13. Sweet Potatoes



14. Watermelon



15. Carrots



Article

The Effect of Household Food Processing on Pesticide Residues in Oranges (*Citrus sinensis*)

Perihan Yolci Omeroglu ^{1,2,*}, Busra Acoglu Celik ¹ and Elif Koc Alibasoglu ¹

¹ Department of Food Engineering, Faculty of Agriculture, Gorukle Campus, Bursa Uludag University, Bursa 16059, Turkey

² Science and Technology Application and Research Center (BITUAM), Gorukle Campus, Bursa Uludag University, Bursa 16059, Turkey

* Correspondence: pyomeroglu@uludag.edu.tr; Tel.: +90-542-423-78-29

Abstract: In this study, the effect of various household food-processing methods (washing, peeling, processing into jam and fruit juice, freezing, storage) on pesticide residues (abamectin, buprofezin, ethoxazole, imazalil, and thiophanate-methyl) in oranges was investigated. Residue analyses were performed by quick-easy-cheap-efficient-rugged-safe (QuEChERS) extraction and liquid chromatography coupled with triple quadrupole mass spectrometry (LC-MS/MS) analysis. The limit of quantification of the method for each pesticide was 10 µg/kg. Physicochemical properties of the pesticides

Washing of oranges with tap water reduced the residues carbendazim, abamectin, imidacloprid, prochloraz, and cypermethrin by 43.6–85.4%.

foods11233918

Academic Editors: Roberto Romero-González, Dapeng Peng and Yongzhong Qian

Received: 6 October 2022

Accepted: 1 December 2022

Published: 5 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Orange (*Citrus sinensis*) is one of the most popular and most-grown citrus families in the world. According to the Turkish Mediterranean Exporters' Association, the citrus group took first place in Turkish total fruit and vegetable exports between 2017 and 2018 (405.2 million tons) [1]. Valencia is the most important orange variety grown in Turkey, and its farming has been increasing rapidly in recent years. Its most important feature is that it can be grown and harvested up to the late months of the spring. The peel of the fruit is slightly rough and moderately thick and the inner skin is thick and contains few seeds. Orange is a good source of vitamins, flavonoids, terpenes, potassium, and calcium, and fulfills most of the daily need for vitamin C for consumers. Orange can be consumed fresh or processed domestically or industrially into jam, marmalade, or fruit juice, in addition to its frozen and dried forms [2]. Orange peel is used as a flavoring agent in the pastry sector and essential oils extracted from the peels are used in the cosmetics industry.

Since citrus fruits are cultivated in warm and subtropical climates where unwanted pests and wild herbs are common, it is normal agricultural practice to use pesticides to increase the yield of the crop [3]. However, excessive and unprescribed spraying and early harvesting can leave residues in the product, which may adversely affect the safety of the food consumed. Pesticide residue levels in foods must be safe for consumers, so national and international authorities have set maximum residue limits (MRL) for fresh fruits and









Fill bottle with
warm water to
fill line



Add Contents of
this refill pouch



Top off with
water, tighten
sprayer
securely



Shake up and
clean with
purpose







What is arguably, the '*most well-known & studied*' environmental trigger for Chronic Inflammatory Diseases?



113,597 DOCTORS FROM COAST TO COAST WERE ASKED!



Family doctors, surgeons, diagnosticians, nose and throat specialists... doctors in every branch of medicine were asked: "What cigarette do you smoke, Doctor?"

Three nationally known independent research organizations did the asking.

The answers came in by the thousands. Actual statements from doctors themselves. Figures were checked and re-checked! The result? Camels... convincingly!

According to this recent Nationwide survey:

MORE DOCTORS SMOKE CAMELS THAN ANY OTHER CIGARETTE!

This is no casual claim. It's an actual fact. Based on the statements of doctors themselves to three nationally known independent research organizations.

THE QUESTION was very simple. One that you...any smoker... might ask a doctor: "What cigarette do you smoke, Doctor?"

After all, doctors are human too. Like you, they smoke for pleasure. Their taste, like yours, enjoys the pleasing flavor of costlier tobaccos. Their throats too appreciate a cool mildness.

And more doctors named Camels than any other cigarette!

If you are a Camel smoker, this preference for Camels among physicians and surgeons will not surprise you. But if you are not now smoking Camels, by all means try them. Compare them critically in your "T-Zone" (see right).

CAMEL-COSTLIER TOBACCOS

THE "T-ZONE" TEST WILL TELL YOU

The "T-Zone"—the taste and throat throat—is your own personal ground for any cigarette. Only your taste and throat can decide which cigarette tastes best to you... how it affects your throat. On the basis of the experience of more, more millions of smokers, we believe Camels will win your "T-Zone" as a "T."





OPEN ACCESS

Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports

Allan Hackshaw,¹ Joan K Morris,² Sadie Boniface,³ Jin-Ling Tang,⁴ Dušan Milenković⁵

¹Cancer Research UK and UCL Cancer Trials Centre, University College London, London W1T 4TJ, UK

²Wolfson Institute of Preventive Medicine, Queen Mary, University of London, London, UK

³Addictions Department, Kings College London, London, UK

⁴JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

⁵Meta Research, Evidera, London, UK (formerly Cancer Research UK and UCL Cancer Trials Centre)

Correspondence to:

ABSTRACT

OBJECTIVE

To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline 1946 to May 2015, with manual searches of references.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective cohort studies with at least 50 events, reporting hazard ratios or relative risks (both hereafter referred to as relative risk) compared with never

smokers. Analyses were done for each combination of sex and disorder.

RESULTS

The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one and 20 cigarettes per day (or 2.19 and 3.95 using relative risks adjusted for multiple factors). Men who smoked one cigarette per day had 46% of the excess relative risk for smoking 20 cigarettes per day (53%

The meta-analysis included 55 publications containing 141 cohort studies (several involved the pooling of multiple studies).

for smoking 20 cigarettes per day ($IRR_{20\text{ per day}} - 1$), expected to be about 5% assuming a linear relation between risk and consumption (as seen with lung cancer). The relative risks for one, five, and 20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate

analyses were done for each combination of sex and disorder. Relative risks were generally higher among women than men.

CONCLUSIONS

Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.

Introduction

Around one billion adults worldwide smoke,¹ with high prevalence in developing countries, where 49% of men and 11% of women use tobacco.² Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth.³ Policies have successfully encouraged people to quit, using aids such as nicotine replacement therapy and electronic cigarettes (e-cigarettes).⁴

In the Health Survey for England (2013 and 2014), 26% of current smokers reported that they wanted to cut consumption down but were not trying to stop, and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking increases the risk of developing coronary heart disease and stroke. Many smokers believe that cutting down the number of cigarettes they smoke substantially reduces their risk of developing tobacco related disorders. Occasional individual studies and a meta-analysis of five studies in 1997 reported that light cigarette smoking (less than five per day) is associated with a higher than expected risk of coronary heart disease.

WHAT THIS STUDY ADDS

Men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke (or 74% and 30%, respectively, when allowing for confounding factors).

The estimates are higher in women: 57% for heart disease and 31% for stroke (or 119% and 46% when allowing for multiple confounders), again compared with never smokers.

People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (coronary heart disease and stroke).



**So what is the true ‘threshold’ in the human body for exposure to cigarette smoke?
When do we cross the line of tolerance**





OPEN ACCESS

Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports

Allan Hackshaw,¹ Joan K Morris,² Sadie Boniface,³ Jin-Ling Tang,⁴ Dušan Milenković⁵

¹Cancer Research UK and UCL Cancer Trials Centre, University College London, London W1T 4TJ, UK

²Wolfson Institute of Preventive Medicine, Queen Mary, University of London, London, UK

³Addictions Department, Kings College London, London, UK

⁴JCSchool of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

⁵Meta Research, Evidera, London, UK (formerly Cancer Research UK and UCL Cancer Trials Centre)

Correspondence to:

ABSTRACT

OBJECTIVE

To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline 1946 to May 2015, with manual searches of references.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective cohort studies with at least 50 events, reporting hazard ratios or relative risks (both hereafter referred to as relative risk) compared with never

analyses were done for each combination of sex and disorder.

RESULTS

The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one and 20 cigarettes per day (or 2.19 and 3.95 using relative risks adjusted for multiple factors). Men who smoked one cigarette per day had 46% of the excess relative risk for smoking 20 cigarettes per day (53%

The excess relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies

for smoking 20 cigarettes per day ($IRR_{20\text{ per day}} - 1$), expected to be about 5% assuming a linear relation between risk and consumption (as seen with lung cancer). The relative risks for one, five, and 20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate

36% using relative risks adjusted for multiple factors). Relative risks were generally higher among women than men.

CONCLUSIONS

Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.

Introduction

Around one billion adults worldwide smoke,¹ with high prevalence in developing countries, where 49% of men and 11% of women use tobacco.² Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth.³ Policies have successfully encouraged people to quit, using aids such as nicotine replacement therapy and electronic cigarettes (e-cigarettes).⁴

In the Health Survey for England (2013 and 2014), 26% of current smokers reported that they wanted to cut consumption down but were not trying to stop, and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking increases the risk of developing coronary heart disease and stroke. Many smokers believe that cutting down the number of cigarettes they smoke substantially reduces their risk of developing tobacco related disorders. Occasional individual studies and a meta-analysis of five studies in 1997 reported that light cigarette smoking (less than five per day) is associated with a higher than expected risk of coronary heart disease.

WHAT THIS STUDY ADDS

Men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke (or 74% and 30%, respectively, when allowing for confounding factors).

The estimates are higher in women: 57% for heart disease and 31% for stroke (or 119% and 46% when allowing for multiple confounders), again compared with never smokers.

People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (coronary heart disease and stroke).





OPEN ACCESS

Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports

Allan Hackshaw,¹ Joan K Morris,² Sadie Boniface,³ Jin-Ling Tang,⁴ Dušan Milenković⁵

¹Cancer Research UK and UCL Cancer Trials Centre, University College London, London W1T 4TJ, UK

²Wolfson Institute of Preventive Medicine, Queen Mary, University of London, London, UK

³Addictions Department, Kings College London, London, UK

⁴JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

⁵Meta Research, Evidera, London, UK (formerly Cancer Research UK and UCL Cancer Trials Centre)

Correspondence to:

ABSTRACT

OBJECTIVE

To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline 1946 to May 2015, with manual searches of references.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective cohort studies with at least 50 events, reporting hazard ratios or relative risks (both hereafter referred to as relative risk) compared with never

analyses were done for each combination of sex and disorder.

RESULTS

The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one and 20 cigarettes per day (or 2.19 and 3.95 using relative risks adjusted for multiple factors). Men who smoked one cigarette per day had 46% of the excess relative risk for smoking 20 cigarettes per day (53%

The excess risk for stroke associated with one cigarette per day (in relation to 20 cigarettes per day) was 41% for men and 34% for women

for smoking 20 cigarettes per day ($RR_{20\text{ per day}} - 1$), expected to be about 5% assuming a linear relation between risk and consumption (as seen with lung cancer). The relative risks for one, five, and 20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate

36% using relative risks adjusted for multiple factors). Relative risks were generally higher among women than men.

CONCLUSIONS

Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.

Introduction

Around one billion adults worldwide smoke,¹ with high prevalence in developing countries, where 49% of men and 11% of women use tobacco.² Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth.³ Policies have successfully encouraged people to quit, using aids such as nicotine replacement therapy and electronic cigarettes (e-cigarettes).⁴

In the Health Survey for England (2013 and 2014), 26% of current smokers reported that they wanted to cut consumption down but were not trying to stop, and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking increases the risk of developing coronary heart disease and stroke. Many smokers believe that cutting down the number of cigarettes they smoke substantially reduces their risk of developing tobacco related disorders. Occasional individual studies and a meta-analysis of five studies in 1997 reported that light cigarette smoking (less than five per day) is associated with a higher than expected risk of coronary heart disease.

WHAT THIS STUDY ADDS

Men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke (or 74% and 30%, respectively, when allowing for confounding factors).

The estimates are higher in women: 57% for heart disease and 31% for stroke (or 119% and 46% when allowing for multiple confounders), again compared with never smokers.

People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (coronary heart disease and stroke).





OPEN ACCESS

Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports

Allan Hackshaw,¹ Joan K Morris,² Sadie Boniface,³ Jin-Ling Tang,⁴ Dušan Milenković⁵

¹Cancer Research UK and UCL Cancer Trials Centre, University College London, London W1T 4TJ, UK

²Wolfson Institute of Preventive Medicine, Queen Mary, University of London, London, UK

³Addictions Department, Kings College London, London, UK

⁴JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

ABSTRACT

OBJECTIVE

To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline 1946 to May 2015, with manual searches of references.

analyses were done for each combination of sex and disorder.

RESULTS

The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one

BMJ: first published as 10.1136/bmj.j5855 on 24

There was no low threshold associated with a safe level of smoking in relation to cardiovascular disease risk, for which even an inhaled PM2.5 dose of 1 mg (one twelfth of a cigarette per day) has an expected relative risk of 1.25 (for CHD).

20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate

Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking increases the risk of developing coronary heart disease and stroke. Many smokers believe that cutting down the number of cigarettes they smoke substantially reduces their risk of developing tobacco related disorders. Occasional individual studies and a meta-analysis of five studies in 1997 reported that light cigarette smoking (less than five per day) is associated with a higher than expected risk of coronary heart disease.

WHAT THIS STUDY ADDS

Men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke (or 74% and 30%, respectively, when allowing for confounding factors).

The estimates are higher in women: 57% for heart disease and 31% for stroke (or 119% and 46% when allowing for multiple confounders), again compared with never smokers.

People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (coronary heart disease and stroke).

Introduction

Around one billion adults worldwide smoke,¹ with high prevalence in developing countries, where 49% of men and 11% of women use tobacco.² Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth.³ Policies have successfully encouraged people to quit, using aids such as nicotine replacement therapy and electronic cigarettes (e-cigarettes).⁴

In the Health Survey for England (2013 and 2014), 26% of current smokers reported that they wanted to cut consumption down but were not trying to stop, and

on 6 May 2022 by guest. Protected by copyright.





OPEN ACCESS

Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports

Allan Hackshaw,¹ Joan K Morris,² Sadie Boniface,³ Jin-Ling Tang,⁴ Dušan Milenković⁵

¹Cancer Research UK and UCL Cancer Trials Centre, University College London, London W1T 4TJ, UK

²Wolfson Institute of Preventive Medicine, Queen Mary, University of London, London, UK

³Addictions Department, Kings College London, London, UK

⁴JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

⁵Meta Research, Evidera, London, UK (formerly Cancer Research UK and UCL Cancer

ABSTRACT

OBJECTIVE

To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline 1946 to May 2015, with manual searches of references.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective cohort studies with at least 50 events

analyses were done for each combination of sex and disorder.

RESULTS

The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one and 20 cigarettes per day (or 2.19 and 3.95 using relative risks adjusted for multiple factors). Men who

We show clearly that no safe level of smoking exists for cardiovascular disease at which light smokers can assume that continuing to smoke does not lead to harm.

between risk and consumption (as seen with lung cancer). The relative risks for one, five, and 20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate

than men.

CONCLUSIONS

Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.

Introduction

Around one billion adults worldwide smoke,¹ with high prevalence in developing countries, where 49% of men and 11% of women use tobacco.² Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth.³ Policies have successfully encouraged people to quit, using aids such as nicotine replacement therapy and electronic cigarettes (e-cigarettes).⁴

In the Health Survey for England (2013 and 2014), 26% of current smokers reported that they wanted to cut consumption down but were not trying to stop, and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking increases the risk of developing coronary heart disease and stroke. Many smokers believe that cutting down the number of cigarettes they smoke substantially reduces their risk of developing tobacco related disorders. Occasional individual studies and a meta-analysis of five studies in 1997 reported that light cigarette smoking (less than five per day) is associated with a higher than expected risk of coronary heart disease.

WHAT THIS STUDY ADDS

Men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke (or 74% and 30%, respectively, when allowing for confounding factors).

The estimates are higher in women: 57% for heart disease and 31% for stroke (or 119% and 46% when allowing for multiple confounders), again compared with never smokers.

People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (coronary heart disease and stroke).





OPEN ACCESS

Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports

Allan Hackshaw,¹ Joan K Morris,² Sadie Boniface,³ Jin-Ling Tang,⁴ Dušan Milenković⁵

¹Cancer Research UK and UCL Cancer Trials Centre, University College London, London W1T 4TJ, UK

²Wolfson Institute of Preventive Medicine, Queen Mary, University of London, London, UK

³Addictions Department, Kings College London, London, UK

⁴JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong

⁵Meta Research, Evidera, London, UK (formerly Cancer Research UK and UCL Cancer Trials Centre)

Correspondence to:

ABSTRACT

OBJECTIVE

To use the relation between cigarette consumption and cardiovascular disease to quantify the risk of coronary heart disease and stroke for light smoking (one to five cigarettes/day).

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Medline 1946 to May 2015, with manual searches of references.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective cohort studies with at least 50 events, reporting hazard ratios or relative risks (both hereafter referred to as relative risk) compared with never

smokers. Analyses were done for each combination of sex and disorder.

RESULTS

The meta-analysis included 55 publications containing 141 cohort studies. Among men, the pooled relative risk for coronary heart disease was 1.48 for smoking one cigarette per day and 2.04 for 20 cigarettes per day, using all studies, but 1.74 and 2.27 among studies in which the relative risk had been adjusted for multiple confounders. Among women, the pooled relative risks were 1.57 and 2.84 for one and 20 cigarettes per day (or 2.19 and 3.95 using relative risks adjusted for multiple factors). Men who smoked one cigarette per day had 46% of the excess relative risk for smoking 20 cigarettes per day (53%

Smokers need to quit completely rather than cut down if they wish to avoid most of the risk associated with heart disease and stroke.

for smoking 20 cigarettes per day ($RR_{20\text{ per day}} - 1$), expected to be about 5% assuming a linear relation between risk and consumption (as seen with lung cancer). The relative risks for one, five, and 20 cigarettes per day were also pooled across all studies in a random effects meta-analysis. Separate

analyses were done for each combination of sex and disorder. Relative risks were generally higher among women than men.

CONCLUSIONS

Smoking only about one cigarette per day carries a risk of developing coronary heart disease and stroke much greater than expected: around half that for people who smoke 20 per day. No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.

Introduction

Around one billion adults worldwide smoke,¹ with high prevalence in developing countries, where 49% of men and 11% of women use tobacco.² Although the prevalence of current smokers has decreased over time in several countries, the global absolute number of smokers has increased owing to population growth.³ Policies have successfully encouraged people to quit, using aids such as nicotine replacement therapy and electronic cigarettes (e-cigarettes).⁴

In the Health Survey for England (2013 and 2014), 26% of current smokers reported that they wanted to cut consumption down but were not trying to stop, and

WHAT IS ALREADY KNOWN ON THIS TOPIC

Smoking increases the risk of developing coronary heart disease and stroke. Many smokers believe that cutting down the number of cigarettes they smoke substantially reduces their risk of developing tobacco related disorders. Occasional individual studies and a meta-analysis of five studies in 1997 reported that light cigarette smoking (less than five per day) is associated with a higher than expected risk of coronary heart disease.

WHAT THIS STUDY ADDS

Men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke (or 74% and 30%, respectively, when allowing for confounding factors).

The estimates are higher in women: 57% for heart disease and 31% for stroke (or 119% and 46% when allowing for multiple confounders), again compared with never smokers.

People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (coronary heart disease and stroke).



So what is the '*threshold*' in the human body for exposure to cigarette smoke without causing platelet and endothelial dysfunction, arterial stiffness, atherosclerosis, oxidative stress, inflammation, heart rate variability, energy metabolism, and increased infarct size ?





Contents lists available at ScienceDirect

Best Practice & Research Clinical
Gastroenterology



9

Non-celiac wheat sensitivity: Differential diagnosis, triggers and implications



Detlef Schuppan, MD, PhD ^{a, b, *}, Geethanjali Pickert, PhD ^a,
Muhammad Ashfaq-Khan, BSc ^a, Victor Zevallos, PhD ^a

^a Institute for Translational Immunology and Research Center for Immunotherapy (FZI), University Medical Center, Johannes Gutenberg University, Mainz, Germany

Wheat amylase-trypsin inhibitors (ATIs) are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in the intestinal mucosa, and have been identified as the most likely triggers of Non-Celiac Wheat Sensitivity.

Rye

strongly indicate that NCWS exists in a substantial proportion of the population, that it is an innate immune reaction to wheat and that patients often present with extraintestinal symptoms, such as worsening of an underlying inflammatory disease in clear association with wheat consumption. **Wheat amylase-trypsin inhibitors (ATIs) have been identified as the most likely triggers of NCWS.** They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa. Non-gluten containing cereals or staples display no or little TLR4 stimulating activity. Wheat ATIs are a family of up to 17 similar proteins of molecular weights around 15 kD and represent 2–4% of the wheat protein. With oral

* Corresponding author. Institute of Translational Immunology, University Medical Center, Johannes Gutenberg University, Langenbeckstr.1, 55131 Mainz, Germany. Tel.: +49 6131 177356; fax: +49 6131 177357.
E-mail address: detlef.schuppan@unimedizin-mainz.de (D. Schuppan).

<http://dx.doi.org/10.1016/j.bpg.2015.04.002>
1521-6918/© 2015 Published by Elsevier Ltd.





Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology



9

Non-celiac wheat sensitivity: Differential diagnosis, triggers and implications



Detlef Schuppan, MD, PhD ^{a, b, *}, Geethanjali Pickert, PhD ^a,
Muhammad Ashfaq-Khan, BSc ^a, Victor Zevallos, PhD ^a

^a Institute for Translational Immunology and Research Center for Immunotherapy (FZI), University Medical Center, Johannes Gutenberg University, Mainz, Germany

^b Celiac Center, Beth Israel Deaconess Medical Center, and Harvard Celiac Center, Harvard Medical School, Boston, MA, USA

ABSTRACT

ATIs directly interact with TLR4 with nanomolar affinity

Dendritic cell
Extraintestinal
Gluten
Intestine
Macrophage
Monocyte
Rye

the major wheat sensitivities, celiac disease and wheat allergy, have to be ruled out which may be difficult for wheat allergy. The non-inflammatory intolerances to carbohydrates, mainly lactose and FODMAPs (fermentable oligi-, di-, monosaccharides and polyols), which cause bloating or diarrhoea, can usually be excluded clinically or by simple tests. Recent studies and experimental data strongly indicate that NCWS exists in a substantial proportion of the population, that it is an innate immune reaction to wheat and that patients often present with extraintestinal symptoms, such as worsening of an underlying inflammatory disease in clear association with wheat consumption. **Wheat amylase-trypsin inhibitors (ATIs) have been identified as the most likely triggers of NCWS.** They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa. Non-gluten containing cereals or staples display no or little TLR4 stimulating activity. Wheat ATIs are a family of up to 17 similar proteins of molecular weights around 15 kD and represent 2–4% of the wheat protein. With oral

* Corresponding author. Institute of Translational Immunology, University Medical Center, Johannes Gutenberg University, Langenbeckstr.1, 55131 Mainz, Germany. Tel.: +49 6131 177356; fax: +49 6131 177357.
E-mail address: detlef.schuppan@unimedizin-mainz.de (D. Schuppan).

<http://dx.doi.org/10.1016/j.bpg.2015.04.002>
1521-6918/© 2015 Published by Elsevier Ltd.



So what is the 'threshold' in the human body for exposure to wheat before activating TLR4?

TLR4 activation by a perceived threat:

- Increases release of zonulin
- Activates NfκB the major 'amplifier' of innate immune response
- Creates and activates both an innate and adaptive immune inflammatory state
- Alters microbiome diversity and richness
- Alters expression of antimicrobial peptide genes
- Impairs epithelial barrier function and reproduction
- Inhibits intestinal lining healing
- Creates intestinal permeability

Initiates production of Memory Bcells against the recognized pathogen for future, *quicker* recognition and response if exposed





Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology



9

Non-celiac wheat sensitivity: Differential diagnosis, triggers and implications



Detlef Schuppan, MD, PhD ^{a, b, *}, Geethanjali Pickert, PhD ^a,
Muhammad Ashfaq-Khan, BSc ^a, Victor Zevallos, PhD ^a

^a Institute for Translational Immunology and Research Center for Immunotherapy (FZI), University Medical Center, Johannes Gutenberg University, Mainz, Germany

^b Celiac Center, Beth Israel Deaconess Medical Center, and Harvard Celiac Center, Harvard Medical School, Boston, MA, USA

ABSTRACT

ATIs directly interact with TLR4 with nanomolar affinity

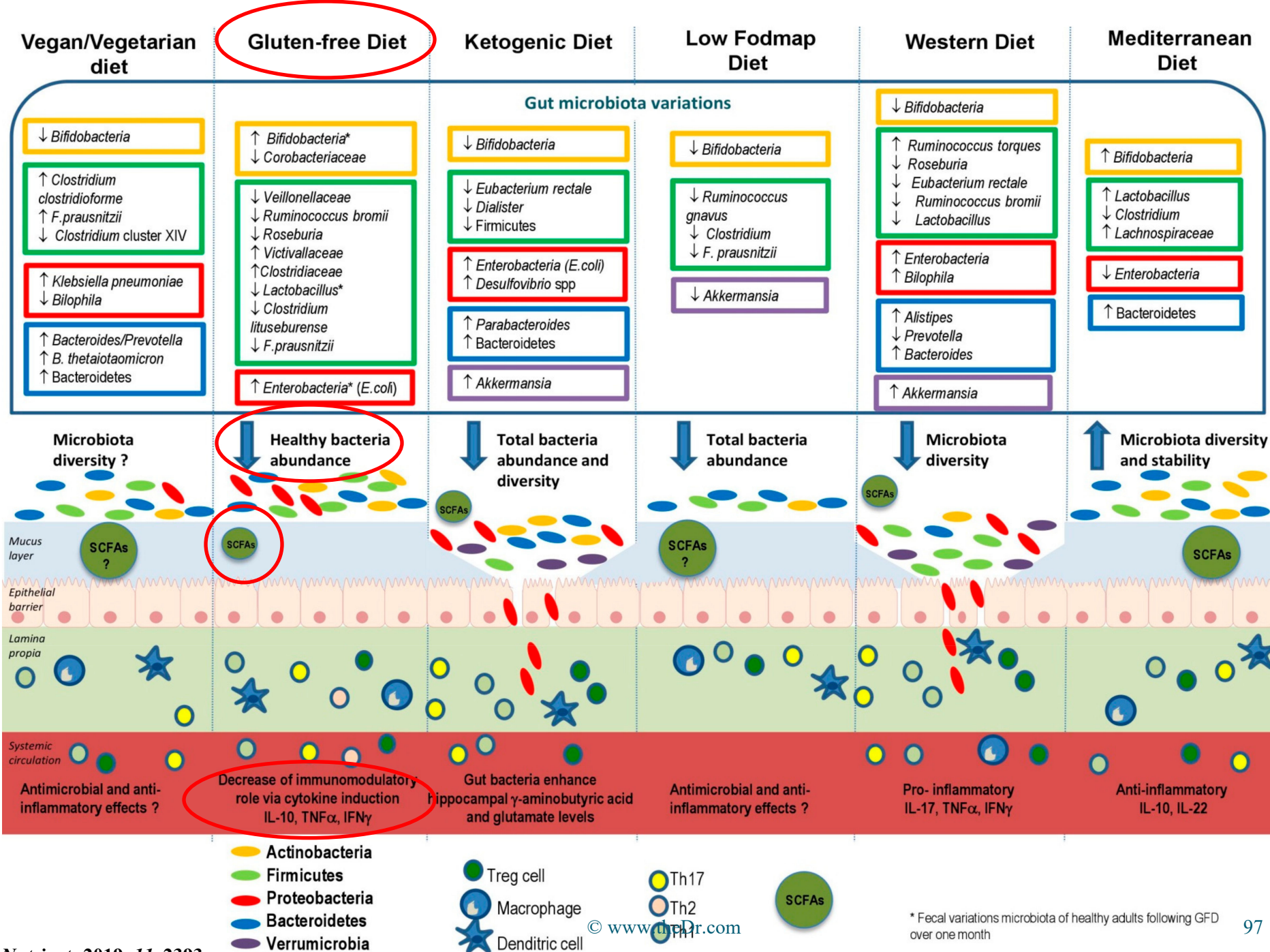
Dendritic cell
Extraintestinal
Gluten
Intestine
Macrophage
Monocyte
Rye

the major wheat sensitivities, celiac disease and wheat allergy, have to be ruled out which may be difficult for wheat allergy. The non-inflammatory intolerances to carbohydrates, mainly lactose and FODMAPs (fermentable oligi-, di-, monosaccharides and polyols), which cause bloating or diarrhoea, can usually be excluded clinically or by simple tests. Recent studies and experimental data strongly indicate that NCWS exists in a substantial proportion of the population, that it is an innate immune reaction to wheat and that patients often present with extraintestinal symptoms, such as worsening of an underlying inflammatory disease in clear association with wheat consumption. **Wheat amylase-trypsin inhibitors (ATIs) have been identified as the most likely triggers of NCWS.** They are highly protease resistant and activate the toll-like receptor 4 (TLR4) complex in monocytes, macrophages and dendritic cells of the intestinal mucosa. Non-gluten containing cereals or staples display no or little TLR4 stimulating activity. Wheat ATIs are a family of up to 17 similar proteins of molecular weights around 15 kD and represent 2–4% of the wheat protein. With oral

* Corresponding author. Institute of Translational Immunology, University Medical Center, Johannes Gutenberg University, Langenbeckstr.1, 55131 Mainz, Germany. Tel.: +49 6131 177356; fax: +49 6131 177357.
E-mail address: detlef.schuppan@unimedizin-mainz.de (D. Schuppan).

<http://dx.doi.org/10.1016/j.bpg.2015.04.002>
1521-6918/© 2015 Published by Elsevier Ltd.





That's
in

I can

But I don't
Every little
feel bad when
I eat wheat

*I can only do my
best, and that will
have to be good
enough*

This is
bulls—

help

Kindly think about this concept of zero tolerance, and how your own brain is responding to this science.

What rationales or justifications pop up in your consciousness to this?

- You are not alone in this response
- This is the same mind chatter that every one of your patients go through as you talk about 'paradigm-shifting information, organics, gluten,...
- By acknowledging the very common resistance that pops up, new avenues, new approaches emerge to deal with resistance in ourselves, and then in our patients

Knowledge alone is cerebral

Knowledge leads to empowerment when action steps

can be implemented



I Know you don't like
hearing this. Here's a
couple of pearls





Mediterranean Gluten-Free Diet: Is It a Fair Bet for the Treatment of Gluten-Related Disorders?

Karla A. Bascuñán^{1,2}, Luca Elli^{1,3}, Maurizio Vecchi^{3,4}, Alice Scricciolo¹, Federica Mascaretti¹, Maria Parisi¹, Luisa Doneda⁵, Vincenza Lombardo¹, Magdalena Araya⁶ and Leda Roncoroni^{1,5*}

¹ Center for Prevention and Diagnosis of Celiac Disease, Gastroenterology and Endoscopy Unit, Fondazione Istituto di Ricovero a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ² Department of Nutrition, School of Medicine, University of Chile, Santiago, Chile; ³ Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; ⁴ General Surgery Unit, Fondazione Istituto di Ricovero a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁵ Department of Biomedical, Surgical, and Dental Sciences, University of Milan, Milan, Italy; ⁶ Institute of Nutrition and Food Technology, Instituto de Nutrición y Tecnología de los Alimentos (INTA), University of Chile, Santiago, Chile

Gluten-free diet (GFD) is the current treatment of gluten-related disorders. It eliminates

Pseudo-cereals are buckwheat, amaranth, quinoa, and chia.

Edited by:

Marco Vincenzo Lenti,
University of Pavia, Italy

Reviewed by:

Claudio Nicoletti,
University of Florence, Italy
Lorenzo Norsa,
Ospedale Papa Giovanni XXIII, Italy

*Correspondence:

Leda Roncoroni
leda.roncoroni@unimi.it

Specialty section:

This article was submitted to
Nutritional Immunology,
a section of the journal
Frontiers in Nutrition

Received: 16 July 2020

Accepted: 04 November 2020

Published: 02 December 2020

Citation:

Bascuñán KA, Elli L, Vecchi M,
Scricciolo A, Mascaretti F, Parisi M,
Doneda L, Lombardo V, Araya M and
Roncoroni L (2020) Mediterranean
Gluten-Free Diet: Is It a Fair Bet for the
Treatment of Gluten-Related
Disorders? Front. Nutr. 7:583981.
doi: 10.3389/fnut.2020.583981

about how to improve GFD's nutritional quality, to make it not only gluten-free, but also healthy. The "Mediterranean diet" (MedD) refers to the dietary pattern and eating habits typical of populations living in the Mediterranean basin, which have been associated with low prevalence of several diet-related pathologies. Here we present a narrative review of the current knowledge about GFD and MedD, their characteristics and central food components. Based on the Mediterranean diet pyramid developed by the Italian pediatric society, we propose a combination between the MedD and the GFD, an attractive alternative to reach a gluten-free state that at the same time is healthy, with a clear benefit to those who practice it.

Keywords: gluten-free diet, Mediterranean diet, food pyramid, cereals, pseudocereals

INTRODUCTION

Gluten related disorders share in common that they are triggered by gluten ingestion. They are a changing group of conditions, including celiac disease (CD), wheat allergy (WA), and non-celiac gluten sensitivity (NCGS) (1). Although mediated by different pathogenic pathways, their clinical manifestations may be similar (2), posing difficulties at the time of diagnosis (3). Their only effective treatment is a gluten-free diet (GFD), which eliminates wheat, rye, and barley consumption. GFD consists of a combination of naturally gluten-free foods (GFF) and gluten-free substitutes prepared with a variety of gluten-free foods and cereals (4). Although highly effective, GFD requires supervision by a trained professional, who must educate the patient and manage the diet, because this is often poor in fiber and vitamins and high in lipid and sugar content (5). In fact, excessive weight and obesity can also be a concern in celiac patients following a GFD, due to the rich-energy gluten-free foods/products commonly eaten (6). Currently available gluten-free products are often low in protein, with high fat and salt content. Higher levels of dietary fiber



HTB Rejuvenate™ Immuno-Rejuvenation Observational Trial

Jeffrey Bland PhD, Arti Chandra MD MPH, Austin Perlmutter MD, Michelle Babb MS RD,
Barbara Schiltz MS RN, Gillian Martin
Clinical Studies Group, Big Bold Health Inc
Bainbridge Island, Washington USA

Abstract

This observational trial examined the subjective impact of HTB Rejuvenate™, a phytochemical-rich dietary supplement, on immune-related health. Eighteen apparently healthy individuals (14 women, 4 men; average age 61 ± 7.5 years) consumed two capsules twice daily (a total of two thousand milligrams) of a dietary supplement formulated with a Himalayan Tartary buckwheat flour blend containing a concentration of its bioactive phytochemicals (HTB Rejuvenate™) for 30 days. Principal bioactive molecules found in the studied supplement included rutin, quercetin, hesperidin, luteolin, diosmin, 2-hydroxybenzylamine (2-HOBA), and hydroxymethylbutyrate (HMB). In previous studies, these molecules have been found to play a role in adaptive immunomodulation, including support for apoptosis,

It is well known that aging of the immune system is related to the epigenetic alteration of methylation patterns of the autophagy genes in macrophage cells.

Background

It is well recognized that the immune system controls function far beyond the protection against infectious disease.¹ Scientific research increasingly supports the involvement of the immune system on diverse aspects of human health and suggests a role for targeted immune modulation in a variety of pathologies, including cancer, cardiovascular disease, mood disorders, autoimmune disease, and infectious disease.² The influence of the immune system on overall health is in part a result of its presence in virtually every organ and tissue of the body, including the blood, intestinal tract, liver, adipose tissue, brain, muscle, respiratory tract, and connective tissue. A better understanding of underlying immunological patterns and their correlations with existing pathological health patterns may help to guide immunological interventions. In addition to pharmaceutical therapies, dietary and supplement-based interventions including vitamins, minerals, and phytochemicals may help shift immunological status towards a more adaptive state.

The makeup and function of the immune system has been shown to reflect and integrate a wide variety of environmental and dietary influences. Alterations in immune system function has been associated with a wide array of symptoms and health-related issues. It is also known that immune system function varies widely among individuals, and this variation is largely driven by non-heritable influences.^{3,4} This suggests that an individual's diet, environment, and other lifestyle factors may have a dominant role in "training" the immune system and could perhaps be more significant than genetic inheritance.

Factors Associated with Immunological Resilience

Aging is associated with decreased immune resilience to infectious and inflammatory diseases. It is now recognized that it is not just the conventional concept of chronological age (as measured in birthdays), but rather the biological age of the immune system that influences its function.⁵ Whereas chronological age is not modifiable, it has been shown that the



HTB Rejuvenate™ Immuno-Rejuvenation Observational Trial

Jeffrey Bland PhD, Arti Chandra MD MPH, Austin Perlmutter MD, Michelle Babb MS RD,
Barbara Schiltz MS RN, Gillian Martin
Clinical Studies Group, Big Bold Health Inc
Bainbridge Island, Washington USA

Abstract

This observational trial examined the subjective impact of HTB Rejuvenate™, a phytochemical-rich dietary supplement, on immune-related health. Eighteen apparently healthy individuals (14 women, 4 men; average age 61 ± 7.5 years) consumed two capsules twice daily (a total of two thousand milligrams) of a dietary supplement formulated with a Himalayan Tartary buckwheat flour blend containing a concentration of its bioactive phytochemicals (HTB Rejuvenate™) for 30 days. Principal bioactive molecules found in the studied supplement included rutin, quercetin, hesperidin, luteolin, diosmin, 2-hydroxybenzylamine (2-HOBA), and hydroxymethylbutyrate (HMB). In previous studies, these molecules have been found to play a role in adaptive immunomodulation, including support for apoptosis,

The flavonoids that have been demonstrated to enhance mitophagy include ...quercetin and rutin have important roles in promoting mitochondrial function in immune cells and serving as “senolytics” in their ability to reduce immune senescence.

pathologies, including cancer, cardiovascular disease, mood disorders, autoimmune disease, and infectious disease.² The influence of the immune system on overall health is in part a result of its presence in virtually every organ and tissue of the body, including the blood, intestinal tract, liver, adipose tissue, brain, muscle, respiratory tract, and connective tissue. A better understanding of underlying immunological patterns and their correlations with existing pathological health patterns may help to guide immunological interventions. In addition to pharmaceutical therapies, dietary and supplement-based interventions including vitamins, minerals, and phytochemicals may help shift immunological status towards a more adaptive state.

varies widely among individuals, and this variation is largely driven by non-heritable influences.^{3,4} This suggests that an individual's diet, environment, and other lifestyle factors may have a dominant role in “training” the immune system and could perhaps be more significant than genetic inheritance.

Factors Associated with Immunological Resilience

Aging is associated with decreased immune resilience to infectious and inflammatory diseases. It is now recognized that it is not just the conventional concept of chronological age (as measured in birthdays), but rather the biological age of the immune system that influences its function.⁵ Whereas chronological age is not modifiable, it has been shown that the



HTB Rejuvenate™ Immuno-Rejuvenation Observational Trial

Jeffrey Bland PhD, Arti Chandra MD MPH, Austin Perlmutter MD, Michelle Babb MS RD,
Barbara Schiltz MS RN, Gillian Martin
Clinical Studies Group, Big Bold Health Inc
Bainbridge Island, Washington USA

Abstract

Among foods with elevated immune-rejuvenating potential, the ancient buckwheat cultivar Himalayan Tartary buckwheat (*Fagopyrum tataricum*) has been found to contain a unique repertoire of relevant phytochemicals. Compared to common buckwheat (*Fagopyrum esculentum*), Himalayan Tartary buckwheat analysis reveals over 100-fold greater levels of the flavonoid rutin and its metabolite quercetin

pathologies, including cancer, cardiovascular disease, mood disorders, autoimmune disease, and infectious disease.² The influence of the immune system on overall health is in part a result of its presence in virtually every organ and tissue of the body, including the blood, intestinal tract, liver, adipose tissue, brain, muscle, respiratory tract, and connective tissue. A better understanding of underlying immunological patterns and their correlations with existing pathological health patterns may help to guide immunological interventions. In addition to pharmaceutical therapies, dietary and supplement-based interventions including vitamins, minerals, and phytochemicals may help shift immunological status towards a more adaptive state.

varies widely among individuals, and this variation is largely driven by non-heritable influences.^{3,4} This suggests that an individual's diet, environment, and other lifestyle factors may have a dominant role in "training" the immune system and could perhaps be more significant than genetic inheritance.

Factors Associated with Immunological Resilience

Aging is associated with decreased immune resilience to infectious and inflammatory diseases. It is now recognized that it is not just the conventional concept of chronological age (as measured in birthdays), but rather the biological age of the immune system that influences its function.⁵ Whereas chronological age is not modifiable, it has been shown that the





Mediterranean Gluten-Free Diet: Is It a Fair Bet for the Treatment of Gluten-Related Disorders?

Karla A. Bascuñán^{1,2}, Luca Elli^{1,3}, Maurizio Vecchi^{3,4}, Alice Scricciolo¹, Federica Mascaretti¹, Maria Parisi¹, Luisa Doneda⁵, Vincenzo Lombardo¹, Magdalena Araya⁶ and Leda Roncoroni^{1,5*}

¹ Center for Prevention and Diagnosis of Celiac Disease, Gastroenterology and Endoscopy Unit, Fondazione Istituto di Ricovero a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, ² Department of Nutrition, School of Medicine, University of Chile, Santiago, Chile, ³ Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, ⁴ General Surgery Unit, Fondazione Istituto di Ricovero a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, ⁵ Department of Biomedical, Surgical, and Dental Sciences, University of Milan, Milan, Italy, ⁶ Institute of Nutrition and Food Technology, Instituto de Nutrición y Tecnología de los Alimentos (INTA), University of Chile, Santiago, Chile

Today there is concern about how to improve GFD's nutritional quality, to make it not only gluten-free, but also healthy.

*Correspondence: Leda Roncoroni
leda.roncoroni@unimi.it

Specialty section:
This article was submitted to
Nutritional Immunology,
a section of the journal
Frontiers in Nutrition

Received: 16 July 2020

Accepted: 04 November 2020

Published: 02 December 2020

Citation:
Bascuñán KA, Elli L, Vecchi M,
Scricciolo A, Mascaretti F, Parisi M,
Doneda L, Lombardo V, Araya M and
Roncoroni L (2020) Mediterranean
Gluten-Free Diet: Is It a Fair Bet for the
Treatment of Gluten-Related
Disorders? Front. Nutr. 7:583981.
doi: 10.3389/fnut.2020.583981

of the current knowledge about GFD and MedD, their characteristics and central food components. Based on the Mediterranean diet pyramid developed by the Italian pediatric society, we propose a combination between the MedD and the GFD, an attractive alternative to reach a gluten-free state that at the same time is healthy, with a clear benefit to those who practice it.

Keywords: gluten-free diet, Mediterranean diet, food pyramid, cereals, pseudocereals

INTRODUCTION

Gluten related disorders share in common that they are triggered by gluten ingestion. They are a changing group of conditions, including celiac disease (CD), wheat allergy (WA), and non-celiac gluten sensitivity (NCGS) (1). Although mediated by different pathogenic pathways, their clinical manifestations may be similar (2), posing difficulties at the time of diagnosis (3). Their only effective treatment is a gluten-free diet (GFD), which eliminates wheat, rye, and barley consumption. GFD consists of a combination of naturally gluten-free foods (GFF) and gluten-free substitutes prepared with a variety of gluten-free foods and cereals (4). Although highly effective, GFD requires supervision by a trained professional, who must educate the patient and manage the diet, because this is often poor in fiber and vitamins and high in lipid and sugar content (5). In fact, excessive weight and obesity can also be a concern in celiac patients following a GFD, due to the rich-energy gluten-free foods/products commonly eaten (6). Currently available gluten-free products are often low in protein, with high fat and salt content. Higher levels of dietary fiber



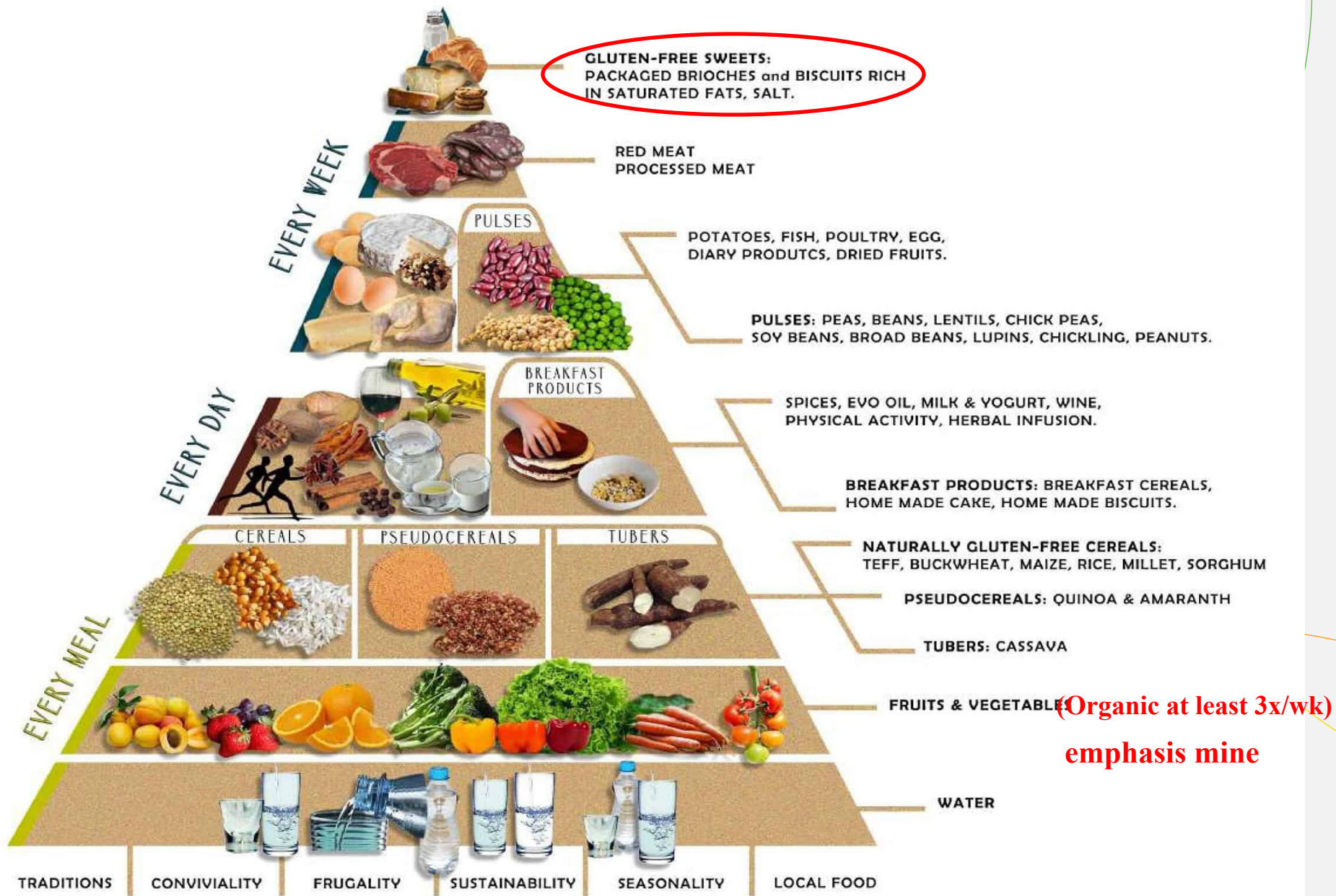


FIGURE 1 | The Mediterranean GFD pyramid: a gluten-free lifestyle. A new graphic representation of the food pyramid based on the MedD is conceived, where coexistence with the GFD is possible. The Mediterranean GFD pyramid gathers updated recommendations considering lifestyle, dietary, sociocultural, environmental, and health challenges of individuals who follow a GFD in the context of healthy eating based on the MedD. MedD, Mediterranean diet; GFD, gluten-free diet.

Western Diet



REVIEW

Open Access

Fast food fever: reviewing the impacts of the Western diet on immunity

Ian A Myles

Abstract

While numerous changes in human lifestyle constitute modern life, our diet has been gaining attention as a potential contributor to the increase in immune-mediated diseases. The Western diet is characterized by an over consumption and reduced variety of refined sugars, salt, and saturated fat. Herein our objective is to detail the mechanisms for the Western diet's impact on immune function. The manuscript reviews the impacts and mechanisms of harm for our over-indulgence in sugar, salt, and fat, as well as the data outlining the impacts of artificial sweeteners, gluten, and genetically modified foods; attention is given to revealing where the literature on the immune impacts of macronutrients is limited to either animal or in vitro models versus where human trials exist. Detailed attention is given to the dietary impact on the gut microbiome and the mechanisms by which our poor dietary choices are encoded into

The Western diet is characterized by a high intake of saturated and omega-6 fatty acids, reduced omega-3 fat intake, an overuse of salt, and too much refined sugar.

damage the heart, kidney, and vasculature; however, it is becoming increasingly clear that the modern diet also damages the immune system. The modern lifestyle is also typified by reduced exposure to microorganisms, increased exposure to pollutions, heightened levels of stress, and a host of other exceptionally well reviewed variables that likely contribute to immune dysfunction [2]. Therefore, while dietary effects on immunity should not be thought of in isolation, herein we focus on the body of evidence detailing the mechanisms for the Western diet's impact on immune function.

Total nutrient intake

Intake of adequate calories and micronutrients is vital for optimal immune function. Deficiency in total calories

occurs at the expense of other proteins from blood and tissues [3]. However, the obesity epidemic clearly outlines that today's diet contains an over abundance of nutrients [1]. While the Western world is not free from micronutrient deficiencies, since this review aims at detailing the immuno-nutrition of a Western diet not typically characterized by micronutrient deficiency, they are thus considered outside the focus. Therefore, we encourage interested readers to seek out lovely review articles on the immune impacts and mechanistic understandings of dietary minerals and vitamins [3-6].

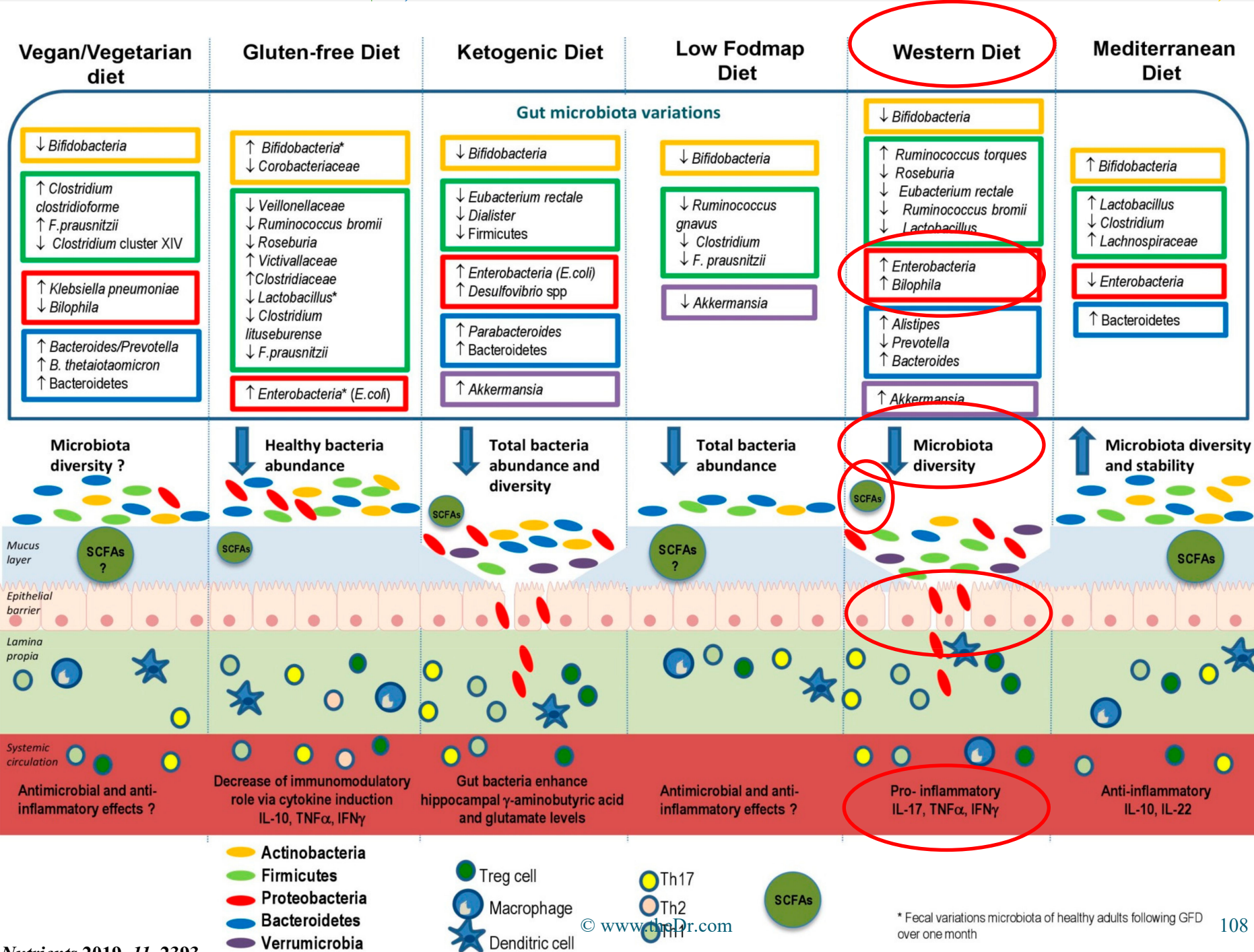
Adipocytes release inflammatory substances including interleukin (IL-) 1, IL-6, and tumor necrosis factor (TNF) [7]. In animal models, it appears that these signals can act as false alarms that, over enough time and in large enough amounts, cause the entire system to dial down its responsiveness – analogous to a person removing a battery from a twitchy smoke detector that frequently alarmed when no signs of fire were present [7,8]. When an actual infection comes along, the response

Correspondence: myles@niaid.nih.gov
Bacterial Pathogenesis Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike Building 33, Room 2W10A, Bethesda, MD, 20892, Maryland



© 2014 Myles; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.





Ketogenic Diet?



Advantages and Disadvantages of the Ketogenic Diet: A Review Article

Jennifer T. Batch¹, Sanjay P. Lamsal², Michelle Adkins³, Senan Sultan⁴, Monica N. Ramirez⁵

1. Internal Medicine, Orange Park Medical Center, Orange Park, USA 2. Radiology, University of Florida Health Jacksonville, Jacksonville, USA 3. Pharmacy, University of Florida, Gainesville, USA 4. Endocrinology, Orange Park Medical Center, Orange Park, USA 5. Pharmacy, University of Florida Health Jacksonville, Jacksonville, USA

Corresponding author: Jennifer T. Batch, jennifer.batchjoudi@hcahealthcare.com

Abstract

The ketogenic diet (KD) has gained immense popularity during the last decade, primarily because of its successful short-term effect on weight loss. In the United States, KD is utilized in a variety of patient populations for weight management, despite limited evidence regarding its efficacy and risks. This literature review provides an evaluation of data on the benefits and risks associated with the chronic use of KD, including its metabolic, endocrinological, and

KD is utilized in a variety of patient populations for weight management, despite limited evidence regarding its efficacy and risks

Body weight is considered to be the normal range, while a BMI of 30.0-34.9 is considered overweight and a BMI ≥ 30 is classified as obese (further classified as obesity class I if BMI is between 30.0-34.9, class II if BMI is between 35.0-39.9, and class III if BMI is ≥ 40.0). In 2016, the World Health Organization (WHO) reported that more than 1.9 billion (39%) adults were overweight globally and of these, over 650 million (13%) were obese [1]. Obesity is associated with multiple comorbidities including type 2 diabetes, hypertension, cardiovascular disease (CVD), cancer, sleep apnea, and obesity-hypoventilation syndrome (OHS). The effectiveness of different types of diets based on different macronutrient restrictions has been a topic of debate for the past few years. Some researchers support restriction in carbohydrate (CHO), while others endorse cutting down protein or fats [2].

This review article will focus on the ketogenic diet KD, which is defined as a low-carbohydrate diet (LCD) with a moderate amount of protein restriction to induce ketosis without restricting fat intake [3]. The concept of KD was initially developed in 1921 by Dr. Russel Wilder for the management of refractory seizures in pediatric patients [4]. Originally, the diet consisted of a 4:1 ratio of fat-to-CHO and protein. Fat provides upwards of 90% the caloric intake [5]. All variations of this diet, whether involving animal- or plant-based derivatives, are based on severely restricting overall intake of CHO with a goal of bringing it down to less than 50 g/day. A well-formulated KD limits protein intake moderately to less than 1 g/lb body weight, or 1.5 g/lb body weight for individuals performing heavy exercises. Additionally, the diet does not restrict fat intake while decreasing appetite and caloric intake, resulting in weight loss observed

Received 07/16/2020
Review began 07/20/2020
Review ended 07/26/2020
Published 08/10/2020

© Copyright 2020
Batch et al. This is an open access
article distributed under the terms of
the Creative Commons Attribution
License CC-BY 4.0., which permits
unrestricted use, distribution, and
reproduction in any medium, provided
the original author and source are
credited.



How to cite this article

Batch J T, Lamsal S P, Adkins M, et al. (August 10, 2020) Advantages and Disadvantages of the Ketogenic Diet: A Review Article. Cureus 12(8): e9639. DOI 10.7759/cureus.9639

Review

The Role of the Gut Microbiota on the Beneficial Effects of Ketogenic Diets

Ilias Attaye ^{*}, Sophie van Oppenraaij, Moritz V. Warmbrunn and Max Nieuwdorp ^{*}

Department of Internal Medicine and Vascular Medicine, Amsterdam University Medical Center, Location Academic Medical Center, 1105 Amsterdam, The Netherlands; sophievoppenraaij@gmail.com (S.v.O.); m.v.warmbrunn@amsterdamumc.nl (M.V.W.)

^{*} Correspondence: i.attaye@amsterdamumc.nl (I.A.); m.nieuwdorp@amsterdamumc.nl (M.N.)

Abstract: The ketogenic diet is a dietary regime focused on strongly reducing carbohydrate intake and increasing fat intake; leading to a state of ketosis. The ketogenic diet has gained much popularity over the years due to its effects on promoting weight loss, increasing insulin sensitivity and reducing dyslipidaemia. All these factors play a crucial role in the development of cardio-metabolic diseases.

The exact mechanism by which a ketogenic diet promotes its beneficial metabolic effects regarding seizure activity, obesity, dyslipidaemia, and insulin resistance remains unknown, but recent evidence points towards a crucial role for the gut microbiota

Matthias Klein

Received: 8 November 2021

Accepted: 28 December 2021

Published: 31 December 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

epilepsy (DRE) for its anticonvulsant effect and is typically composed of a 4:1 ratio of fat (in grams) to protein plus carbohydrates (in grams), thus shifting the predominant caloric source from carbohydrates to fat [2]. However, there are variations of this diet in which this fat to protein and carbohydrate ratio differs (e.g., modified Atkins diet, low glycemic index treatment, and medium-chain triglyceride diet) [2,3]. Another variation is the very low-calorie ketogenic diet (VLCKD) has been recently proposed as an appealing nutritional strategy for obesity management. The VLCKD is characterized by a low carbohydrate content (<50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and a daily intake of about 500–800 calories [4].

In recent years the ketogenic diet has gained much of its former position back as a potential method to promote weight loss and reduce insulin resistance in both type 1 and type 2 diabetes [5–7]. However, concerns also exist about the long-term efficacy in weight loss and the potential adverse effects on renal function and blood lipid levels due to increased intake of protein and fat [7]. Especially in diabetes, increased animal protein, but not plant protein intake has been associated with insulin resistance and increased morbidity [8,9]. Mechanisms of these results are largely unknown. However, a possible mechanism might be that the regulation of glucose and insulin levels could be undermined due to phosphorylation that is caused by branched-chain and aromatic amino acids, which are mainly derived from animal protein [9–12]. In addition, foods high in animal protein also contain





Ketogenic Diets and Chronic Disease: Weighing the Benefits Against the Risks

Lee Crosby^{1*}, Brenda Davis², Shivam Joshi^{3,4}, Meghan Jardine¹, Jennifer Paul^{1,5,6}, Maggie Neola¹ and Neal D. Barnard^{1,7}

¹Physicians Committee for Responsible Medicine, Washington, DC, United States, ²Brenda Davis Nutrition Consulting, Kelowna, BC, Canada, ³Department of Medicine, New York University Grossman School of Medicine, New York, NY, United States, ⁴Department of Medicine, New York City Health + Hospitals/Bellevue, New York, NY, United States, ⁵College of Liberal and Professional Studies, University of Pennsylvania, Philadelphia, PA, United States, ⁶School of Public Health, Loma Linda University, Loma Linda, CA, United States, ⁷Adjunct Faculty, Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, United States

Ketogenic diets can cause fatigue, headache, nausea, constipation, hypoglycemia, and acidosis, especially within the first few days to weeks of following the diet

Maria Montserrat Diaz Pedrosa,
State University of Maringá, Brazil
Meghit Boumediene Khaled,
University of Sidi-Bel-Abbès, Algeria

*Correspondence:
Lee Crosby
LCrosby@pcrm.org

Specialty section:
This article was submitted to
Clinical Nutrition,
a section of the journal
Frontiers in Nutrition

Received: 29 April 2021
Accepted: 10 June 2021
Published: 16 July 2021

Citation:
Crosby L, Davis B, Joshi S, Jardine M,
Paul J, Neola M and Barnard ND
(2021) Ketogenic Diets and Chronic
Disease: Weighing the Benefits
Against the Risks.
Front. Nutr. 8:702802.
doi: 10.3389/fnut.2021.702802

may outweigh the benefits.

Keywords: ketogenic diet, very-low-carbohydrate diet, low-carbohydrate diet, obesity, disease prevention

INTRODUCTION

Very-low-carbohydrate (ketogenic) diets have been promoted for weight loss and, less commonly, for other health reasons. This review summarizes the effects of a ketogenic diet on health conditions for which it has been promoted, as well as potential long-term effects on health.

The term “ketogenic diet” generally refers to a diet that is very low in carbohydrate, modest in protein, and high in fat. This mix of fuels aims to induce *ketosis*, or the production of ketone bodies that serve as an alternate energy source for neurons and other cell types that cannot directly metabolize fatty acids. Urinary ketone levels are often used as an indicator of dietary adherence (1).

Various ketogenic diets have been studied, as shown in **Table 1**. The best defined and studied is sometimes called a “classic” ketogenic diet, referring to a very-low-carbohydrate diet that is generally medically supervised, with a 4:1 or 3:1 ratio, by weight, of dietary fat to combined dietary protein and carbohydrate (2).

Other variants allow more protein or carbohydrate (2). Ketogenic diets as typically implemented in scientific studies limit dietary carbohydrate to <50 g per day with varying amounts of fat and protein (3, 4). “Low-carbohydrate diets” refer to carbohydrate intake below the recommended dietary allowance of 130 g/day (3), which may not be low enough to induce ketosis (5).





Ketogenic Diets and Chronic Disease: Weighing the Benefits Against the Risks

Lee Crosby^{1*}, Brenda Davis², Shivam Joshi^{3,4}, Meghan Jardine¹, Jennifer Paul^{1,5,6}, Maggie Neola¹ and Neal D. Barnard^{1,7}

¹Physicians Committee for Responsible Medicine, Washington, DC, United States, ²Brenda Davis Nutrition Consulting, Kelowna, BC, Canada, ³Department of Medicine, New York University Grossman School of Medicine, New York, NY, United States, ⁴Department of Medicine, New York City Health + Hospitals/Bellevue, New York, NY, United States, ⁵College of Liberal and Professional Studies, University of Pennsylvania, Philadelphia, PA, United States, ⁶School of Public Health, Loma Linda University, Loma Linda, CA, United States, ⁷Adjunct Faculty, Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, United States

Dehydration, hepatitis, pancreatitis, hypertriglyceridemia, hyperuricemia, hypercholesterolemia, hypomagnesemia, and hyponatremia can also occur.

Maria Montserrat Diaz Pedrosa,
State University of Maringá, Brazil
Meghit Boumediene Khaled,
University of Sidi-Bel-Abbès, Algeria

*Correspondence:
Lee Crosby
LCrosby@pcrm.org

Specialty section:
This article was submitted to
Clinical Nutrition,
a section of the journal
Frontiers in Nutrition

Received: 29 April 2021
Accepted: 10 June 2021
Published: 16 July 2021

Citation:
Crosby L, Davis B, Joshi S, Jardine M,
Paul J, Neola M and Barnard ND
(2021) Ketogenic Diets and Chronic
Disease: Weighing the Benefits
Against the Risks.
Front. Nutr. 8:702802.
doi: 10.3389/fnut.2021.702802

may outweigh the benefits.

Keywords: ketogenic diet, very-low-carbohydrate diet, low-carbohydrate diet, obesity, disease prevention

INTRODUCTION

Very-low-carbohydrate (ketogenic) diets have been promoted for weight loss and, less commonly, for other health reasons. This review summarizes the effects of a ketogenic diet on health conditions for which it has been promoted, as well as potential long-term effects on health.

The term “ketogenic diet” generally refers to a diet that is very low in carbohydrate, modest in protein, and high in fat. This mix of fuels aims to induce *ketosis*, or the production of ketone bodies that serve as an alternate energy source for neurons and other cell types that cannot directly metabolize fatty acids. Urinary ketone levels are often used as an indicator of dietary adherence (1).

Various ketogenic diets have been studied, as shown in **Table 1**. The best defined and studied is sometimes called a “classic” ketogenic diet, referring to a very-low-carbohydrate diet that is generally medically supervised, with a 4:1 or 3:1 ratio, by weight, of dietary fat to combined dietary protein and carbohydrate (2).

Other variants allow more protein or carbohydrate (2). Ketogenic diets as typically implemented in scientific studies limit dietary carbohydrate to <50 g per day with varying amounts of fat and protein (3, 4). “Low-carbohydrate diets” refer to carbohydrate intake below the recommended dietary allowance of 130 g/day (3), which may not be low enough to induce ketosis (5).





Ketogenic Diets and Chronic Disease: Weighing the Benefits Against the Risks

Lee Crosby^{1*}, Brenda Davis², Shivam Joshi^{3,4}, Meghan Jardine¹, Jennifer Paul^{1,5,6}, Maggie Neola¹ and Neal D. Barnard^{1,7}

¹ Physicians Committee for Responsible Medicine, Washington, DC, United States, ² Brenda Davis Nutrition Consulting, Kelowna, BC, Canada, ³ Department of Medicine, New York University Grossman School of Medicine, New York, NY, United States, ⁴ Department of Medicine, New York City Health + Hospitals/Bellevue, New York, NY, United States, ⁵ College of Liberal and Professional Studies, University of Pennsylvania, Philadelphia, PA, United States, ⁶ School of Public Health, Loma Linda University, Loma Linda, CA, United States, ⁷ Adjunct Faculty, Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, United States

Longer-term effects can include decreased bone mineral density, nephrolithiasis, cardiomyopathy, anemia, and neuropathy of the optic nerve

Maria Montserrat Diaz Pedrosa,
State University of Maringá, Brazil
Meghit Boumediene Khaled,
University of Sidi-Bel-Abbès, Algeria

*Correspondence:
Lee Crosby
LCrosby@pcrm.org

Specialty section:
This article was submitted to
Clinical Nutrition,
a section of the journal
Frontiers in Nutrition

Received: 29 April 2021
Accepted: 10 June 2021
Published: 16 July 2021

Citation:
Crosby L, Davis B, Joshi S, Jardine M,
Paul J, Neola M and Barnard ND
(2021) Ketogenic Diets and Chronic
Disease: Weighing the Benefits
Against the Risks.
Front. Nutr. 8:702802.
doi: 10.3389/fnut.2021.702802

may outweigh the benefits.

Keywords: ketogenic diet, very-low-carbohydrate diet, low-carbohydrate diet, obesity, disease prevention

INTRODUCTION

Very-low-carbohydrate (ketogenic) diets have been promoted for weight loss and, less commonly, for other health reasons. This review summarizes the effects of a ketogenic diet on health conditions for which it has been promoted, as well as potential long-term effects on health.

The term “ketogenic diet” generally refers to a diet that is very low in carbohydrate, modest in protein, and high in fat. This mix of fuels aims to induce *ketosis*, or the production of ketone bodies that serve as an alternate energy source for neurons and other cell types that cannot directly metabolize fatty acids. Urinary ketone levels are often used as an indicator of dietary adherence (1).

Various ketogenic diets have been studied, as shown in **Table 1**. The best defined and studied is sometimes called a “classic” ketogenic diet, referring to a very-low-carbohydrate diet that is generally medically supervised, with a 4:1 or 3:1 ratio, by weight, of dietary fat to combined dietary protein and carbohydrate (2).

Other variants allow more protein or carbohydrate (2). Ketogenic diets as typically implemented in scientific studies limit dietary carbohydrate to <50 g per day with varying amounts of fat and protein (3, 4). “Low-carbohydrate diets” refer to carbohydrate intake below the recommended dietary allowance of 130 g/day (3), which may not be low enough to induce ketosis (5).



Review

The Role of the Gut Microbiota on the Beneficial Effects of Ketogenic Diets

Ilias Attaye * , Sophie van Oppenraaij, Moritz V. Warmbrunn  and Max Nieuwdorp *

Department of Internal Medicine and Vascular Medicine, Amsterdam University Medical Center, Location Academic Medical Center, 1105 Amsterdam, The Netherlands; sophievoppenraaij@gmail.com (S.v.O.); m.v.warmbrunn@amsterdamumc.nl (M.V.W.)

* Correspondence: i.attaye@amsterdamumc.nl (I.A.); m.nieuwdorp@amsterdamumc.nl (M.N.)

Abstract: The ketogenic diet is a dietary regime focused on strongly reducing carbohydrate intake and increasing fat intake; leading to a state of ketosis. The ketogenic diet has gained much popularity over the years due to its effects on promoting weight loss, increasing insulin sensitivity and reducing dyslipidaemia. All these factors play a crucial role in the development of cardio-metabolic diseases.

A ketogenic diet reduced overall alpha diversity, while increasing the relative abundance of *Akkermansia muciniphila*. This is of note, since a reduced alpha diversity is generally associated with worsened metabolic outcomes, whereas high abundance of *A. muciniphila*, a known short-chain fatty acid (SCFA) producer, is associated with improved metabolic health

iations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

content (<50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and a daily intake of about 500–800 calories [4].

In recent years the ketogenic diet has gained much of its former position back as a potential method to promote weight loss and reduce insulin resistance in both type 1 and type 2 diabetes [5–7]. However, concerns also exist about the long-term efficacy in weight loss and the potential adverse effects on renal function and blood lipid levels due to increased intake of protein and fat [7]. Especially in diabetes, increased animal protein, but not plant protein intake has been associated with insulin resistance and increased morbidity [8,9]. Mechanisms of these results are largely unknown. However, a possible mechanism might be that the regulation of glucose and insulin levels could be undermined due to phosphorylation that is caused by branched-chain and aromatic amino acids, which are mainly derived from animal protein [9–12]. In addition, foods high in animal protein also contain

Advantages and Disadvantages of the Ketogenic Diet: A Review Article

Jennifer T. Batch ¹, Sanjay P. Lamsal ², Michelle Adkins ³, Senan Sultan ⁴, Monica N. Ramirez ⁵

1. Internal Medicine, Orange Park Medical Center, Orange Park, USA 2. Radiology, University of Florida Health Jacksonville, Jacksonville, USA 3. Pharmacy, University of Florida, Gainesville, USA 4. Endocrinology, Orange Park Medical Center, Orange Park, USA 5. Pharmacy, University of Florida Health Jacksonville, Jacksonville, USA

Corresponding author: Jennifer T. Batch, jennifer.batchjoudi@hcahealthcare.com

Abstract

The ketogenic diet (KD) has gained immense popularity during the last decade, primarily because of its successful short-term effect on weight loss. In the United States, KD is utilized in a variety of patient populations for weight management, despite limited evidence regarding its efficacy and risks. This literature review provides an evaluation of data on the benefits and risks associated with the chronic use of KD, including its metabolic, endocrinological, and cardiovascular effects.

Long-term side effects include hepatic steatosis, kidney stones, hypoproteinemia, and vitamin deficiency.

Obesity is classified based on the body mass index (BMI) of the individual. A BMI of 18.5-24.9 kg/m² is considered to be the normal range, while a BMI of 25.0-29.9 is considered overweight and a BMI ≥30 is classified as obese (further classified as obesity class I if BMI is between 30.0-34.9, class II if BMI is between 35.0-39.9, and class III if BMI is ≥40.0). In 2016, the World Health Organization (WHO) reported that more than 1.9 billion (39%) adults were overweight globally and of these, over 650 million (13%) were obese [1]. Obesity is associated with multiple comorbidities including type 2 diabetes, hypertension, cardiovascular disease (CVD), cancer, sleep apnea, and obesity-hypoventilation syndrome (OHS). The effectiveness of different types of diets based on different macronutrient restrictions has been a topic of debate for the past few years. Some researchers support restriction in carbohydrate (CHO), while others endorse cutting down protein or fats [2].

This review article will focus on the ketogenic diet KD, which is defined as a low-carbohydrate diet (LCD) with a moderate amount of protein restriction to induce ketosis without restricting fat intake [3]. The concept of KD was initially developed in 1921 by Dr. Russel Wilder for the management of refractory seizures in pediatric patients [4]. Originally, the diet consisted of a 4:1 ratio of fat-to-CHO and protein. Fat provides upwards of 90% the caloric intake [5]. All variations of this diet, whether involving animal- or plant-based derivatives, are based on severely restricting overall intake of CHO with a goal of bringing it down to less than 50 g/day. A well-formulated KD limits protein intake moderately to less than 1 g/lb body weight, or 1.5 g/lb body weight for individuals performing heavy exercises. Additionally, the diet does not restrict fat intake while decreasing appetite and caloric intake, resulting in weight loss observed

Received 07/16/2020
Review began 07/20/2020
Review ended 07/26/2020
Published 08/10/2020

© Copyright 2020
Batch et al. This is an open access
article distributed under the terms of
the Creative Commons Attribution
License CC-BY 4.0., which permits
unrestricted use, distribution, and
reproduction in any medium, provided
the original author and source are
credited.



How to cite this article

Batch J T, Lamsal S P, Adkins M, et al. (August 10, 2020) Advantages and Disadvantages of the Ketogenic Diet: A Review Article. Cureus 12(8): e9639. DOI 10.7759/cureus.9639

Review

The Role of the Gut Microbiota on the Beneficial Effects of Ketogenic Diets

Ilias Attaye , Sophie van Oppenraaij, Moritz V. Warmbrunn  and Max Nieuwdorp *

Department of Internal Medicine and Vascular Medicine, Amsterdam University Medical Center, Location Academic Medical Center, 1105 Amsterdam, The Netherlands; sophievoppenraaij@gmail.com (S.v.O.); m.v.warmbrunn@amsterdamumc.nl (M.V.W.)

* Correspondence: i.attaye@amsterdamumc.nl (I.A.); m.nieuwdorp@amsterdamumc.nl (M.N.)

Abstract: The ketogenic diet is a dietary regime focused on strongly reducing carbohydrate intake and increasing fat intake; leading to a state of ketosis. The ketogenic diet has gained much popularity over the years due to its effects on promoting weight loss, increasing insulin sensitivity and reducing dyslipidaemia. All these factors play a crucial role in the development of cardio-metabolic diseases; one of the greatest health challenges of the time. Moreover, the ketogenic diet has been known to reduce (epileptic) seizure activity. It is still poorly understood how following a ketogenic diet can lead to these beneficial metabolic effects. However, in recent years it has become clear that diet and the

Diets high in animal protein are linked to gut microbially produced metabolites that are associated with insulin resistance and cardiovascular morbidity

doi.org/10.3390/nu14010191

Academic Editors: Jane Shearer,
Marina Mourtzakis and
Matthias Klein

Received: 8 November 2021

Accepted: 28 December 2021

Published: 31 December 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

ketogenic diet is a dietary regime focused on strongly reducing carbohydrate intake and increasing fat intake; leading to a state of ketosis. The ketogenic diet has gained much popularity over the years due to its effects on promoting weight loss, increasing insulin sensitivity and reducing dyslipidaemia. All these factors play a crucial role in the development of cardio-metabolic diseases; one of the greatest health challenges of the time. Moreover, the ketogenic diet has been known to reduce (epileptic) seizure activity. It is still poorly understood how following a ketogenic diet can lead to these beneficial metabolic effects. However, in recent years it has become clear that diet and the

In recent years the ketogenic diet has gained much of its former position back as a potential method to promote weight loss and reduce insulin resistance in both type 1 and type 2 diabetes [5–7]. However, concerns also exist about the long-term efficacy in weight loss and the potential adverse effects on renal function and blood lipid levels due to increased intake of protein and fat [7]. Especially in diabetes, increased animal protein, but not plant protein intake has been associated with insulin resistance and increased morbidity [8,9]. Mechanisms of these results are largely unknown. However, a possible mechanism might be that the regulation of glucose and insulin levels could be undermined due to phosphorylation that is caused by branched-chain and aromatic amino acids, which are mainly derived from animal protein [9–12]. In addition, foods high in animal protein also contain



Advantages and Disadvantages of the Ketogenic Diet: A Review Article

Jennifer T. Batch¹, Sanjay P. Lamsal², Michelle Adkins³, Senan Sultan⁴, Monica N. Ramirez⁵

1. Internal Medicine, Orange Park Medical Center, Orange Park, USA 2. Radiology, University of Florida Health Jacksonville, Jacksonville, USA 3. Pharmacy, University of Florida, Gainesville, USA 4. Endocrinology, Orange Park Medical Center, Orange Park, USA 5. Pharmacy, University of Florida Health Jacksonville, Jacksonville, USA

Corresponding author: Jennifer T. Batch, jennifer.batchjoudi@hcahealthcare.com

Based on our review, within the first 6-12 months of initiating KD, transient decreases in blood pressure, triglycerides, and glycosylated hemoglobin, as well as increases in HDL and weight loss may be observed. However, the aforementioned effects are generally not seen after 12 months of therapy

overweight globally and of these, over 650 million (13%) were obese [1]. Obesity is associated with multiple comorbidities including type 2 diabetes, hypertension, cardiovascular disease (CVD), cancer, sleep apnea, and obesity-hypoventilation syndrome (OHS). The effectiveness of different types of diets based on different macronutrient restrictions has been a topic of debate for the past few years. Some researchers support restriction in carbohydrate (CHO), while others endorse cutting down protein or fats [2].

This review article will focus on the ketogenic diet KD, which is defined as a low-carbohydrate diet (LCD) with a moderate amount of protein restriction to induce ketosis without restricting fat intake [3]. The concept of KD was initially developed in 1921 by Dr. Russel Wilder for the management of refractory seizures in pediatric patients [4]. Originally, the diet consisted of a 4:1 ratio of fat-to-CHO and protein. Fat provides upwards of 90% the caloric intake [5]. All variations of this diet, whether involving animal- or plant-based derivatives, are based on severely restricting overall intake of CHO with a goal of bringing it down to less than 50 g/day. A well-formulated KD limits protein intake moderately to less than 1 g/lb body weight, or 1.5 g/lb body weight for individuals performing heavy exercises. Additionally, the diet does not restrict fat intake while decreasing appetite and caloric intake, resulting in weight loss observed

Received 07/16/2020

Review began 07/20/2020

Review ended 07/26/2020

Published 08/10/2020

© Copyright 2020

Batch et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

How to cite this article

Batch J T, Lamsal S P, Adkins M, et al. (August 10, 2020) Advantages and Disadvantages of the Ketogenic Diet: A Review Article. Cureus 12(8): e9639. DOI 10.7759/cureus.9639



Review

The Role of the Gut Microbiota on the Beneficial Effects of Ketogenic Diets

Ilias Attaye , Sophie van Oppenraaij, Moritz V. Warmbrunn  and Max Nieuwdorp *

Department of Internal Medicine and Vascular Medicine, Amsterdam University Medical Center, Location Academic Medical Center, 1105 Amsterdam, The Netherlands; sophievoppenraaij@gmail.com (S.v.O.); m.v.warmbrunn@amsterdamumc.nl (M.V.W.)

* Correspondence: i.attaye@amsterdamumc.nl (I.A.); m.nieuwdorp@amsterdamumc.nl (M.N.)

Abstract: The ketogenic diet is a dietary regime focused on strongly reducing carbohydrate intake and increasing fat intake; leading to a state of ketosis. The ketogenic diet has gained much popularity

Multiple studies in epileptic patients showed that a ketogenic diet intervention (4:1) can indeed alter gut microbial composition. Despite the reduction of seizure frequency, gut microbiota composition showed a reduction in healthy bacteria upon a ketogenic diet.

Academic Editors: Jane Shearer, Marina Mourtzakis and Matthias Klein

Received: 8 November 2021

Accepted: 28 December 2021

Published: 31 December 2021

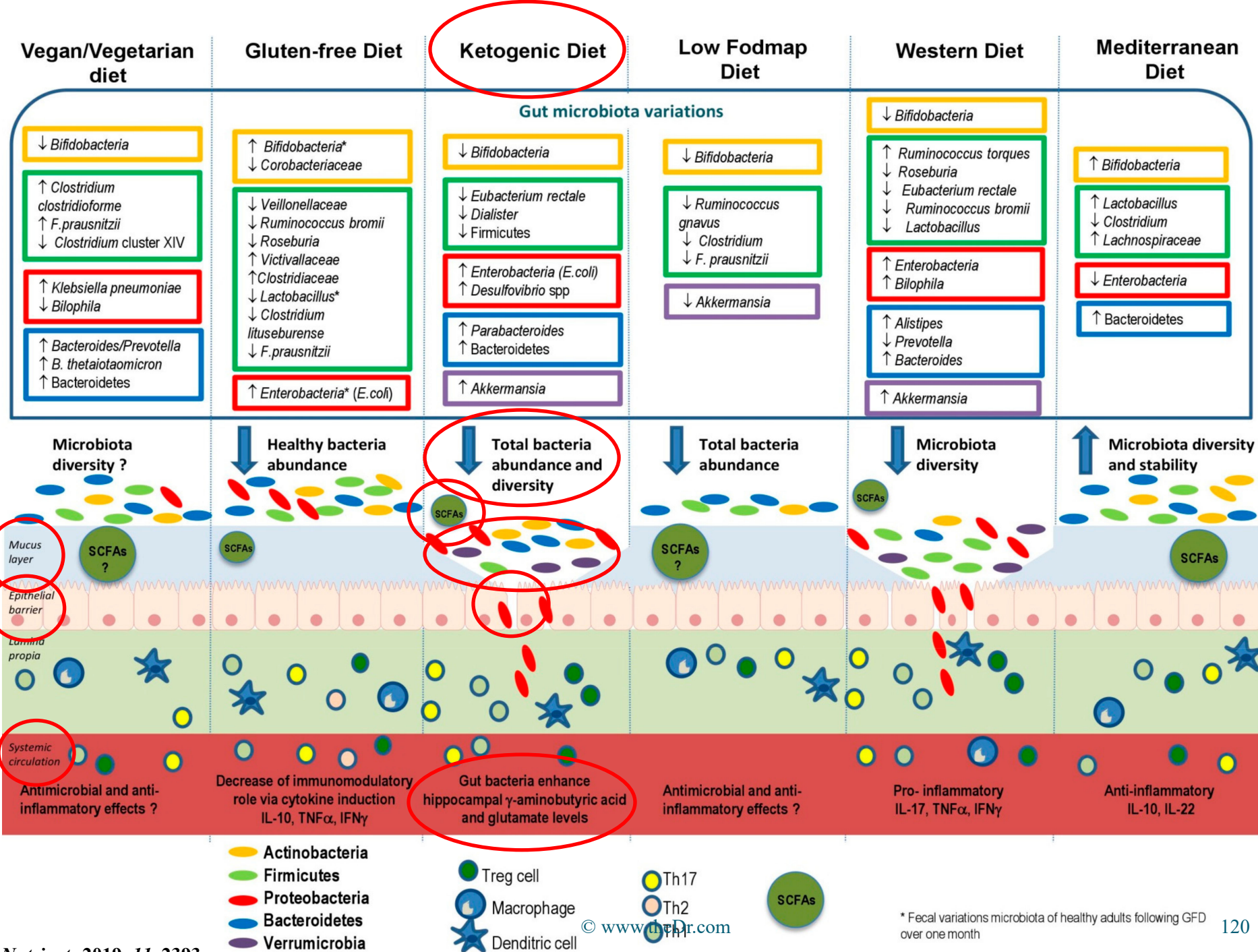
Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

been used to treat epilepsy in children continuously since 1921. CKD is a normocaloric high-fat very low-carbohydrate diet, used worldwide for the treatment of drug-resistant epilepsy (DRE) for its anticonvulsant effect and is typically composed of a 4:1 ratio of fat (in grams) to protein plus carbohydrates (in grams), thus shifting the predominant caloric source from carbohydrates to fat [2]. However, there are variations of this diet in which this fat to protein and carbohydrate ratio differs (e.g., modified Atkins diet, low glycemic index treatment, and medium-chain triglyceride diet) [2,3]. Another variation is the very low-calorie ketogenic diet (VLCKD) has been recently proposed as an appealing nutritional strategy for obesity management. The VLCKD is characterized by a low carbohydrate content (<50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and a daily intake of about 500–800 calories [4].

In recent years the ketogenic diet has gained much of its former position back as a potential method to promote weight loss and reduce insulin resistance in both type 1 and type 2 diabetes [5–7]. However, concerns also exist about the long-term efficacy in weight loss and the potential adverse effects on renal function and blood lipid levels due to increased intake of protein and fat [7]. Especially in diabetes, increased animal protein, but not plant protein intake has been associated with insulin resistance and increased morbidity [8,9]. Mechanisms of these results are largely unknown. However, a possible mechanism might be that the regulation of glucose and insulin levels could be undermined due to phosphorylation that is caused by branched-chain and aromatic amino acids, which are mainly derived from animal protein [9–12]. In addition, foods high in animal protein also contain



Vegan and Vegetarian Diets





The Effects of Vegetarian and Vegan Diets on Gut Microbiota

Aleksandra Tomova^{1*}, Igor Bukovsky², Emilie Rembert³, Willy Yonas³, Jihad Alwarith³, Neal D. Barnard^{3,4} and Hana Kahleova³

¹ Faculty of Medicine, Institute of Physiology, Comenius University in Bratislava, Bratislava, Slovakia, ² Center for Clinical Nutrition, Bratislava, Slovakia, ³ Physicians Committee for Responsible Medicine, Washington, DC, United States, ⁴ Adjunct Faculty, George Washington University School of Medicine and Health Sciences, Washington, DC, United States

The difference in gut microbiota composition between individuals following vegan or vegetarian diets and those following omnivorous diets is well documented. A plant-based diet appears to be beneficial for human health by promoting the development of more diverse and stable microbial systems. Additionally, vegans and vegetarians have significantly higher counts of certain *Bacteroidetes*-related operational taxonomic units

The difference in gut microbiota composition between individuals following vegan or vegetarian diets and those following omnivorous diets is well documented.

Azienda Ospedaliera Universitaria
Federico II, Italy
Christine Ann Butts,
The New Zealand Institute for Plant &
Food Research Ltd, New Zealand

***Correspondence:**

Aleksandra Tomova
aleksandra.tomova@med.uniba.sk

Specialty section:

This article was submitted to
Clinical Nutrition,
a section of the journal
Frontiers in Nutrition

Received: 11 January 2019

Accepted: 29 March 2019

Published: 17 April 2019

Citation:

Tomova A, Bukovsky I, Rembert E,
Yonas W, Alwarith J, Barnard ND and
Kahleova H (2019) The Effects of
Vegetarian and Vegan Diets on Gut
Microbiota. *Front. Nutr.* 6:47.
doi: 10.3389/fnut.2019.00047

vegetarian/vegan diet is effective in promoting a diverse ecosystem of beneficial bacteria to support both human gut microbiome and overall health. This review will focus on effects of different diets and nutrient contents, particularly plant-based diets, on the gut microbiota composition and production of microbial metabolites affecting the host health.

Keywords: gut microbiota, fiber, nutrition, plant-based diet, postbiotics

INTRODUCTION

Recent studies of the human microbiome have emerged as an area of popular interest. For decades, many investigations have elucidated the impact of the human gut microbiota on the physiology of the host, with new and unexpectedly broad implications for health and disease.

The human microbiota, defined as the total of all microbial taxa associated with human beings (bacteria, viruses, fungi, protozoa, archaea), consists of a newly estimated 3×10^{13} (trillion) microbes harbored by each person (1). The term *microbiome* is often incorrectly used interchangeably with the term microbiota. However, microbiome refers to the catalog of these microbes and their genes. The human gut microbiome represents ~ 3.3 million non-redundant microbial genes, which outnumber the human genome of some 21,000 genes in the ratio of $\sim 150:1$ (2). Interestingly, the diversity among the microbiomes of two different individuals is vast compared to their human genomic variation; humans are about 99.9% identical to each other in terms of their genome (3), but their gut microbiome can be up to 80–90% different (4).



Review

Food Components and Dietary Habits: Keys for a Healthy Gut Microbiota Composition

Emanuele Rinninella ^{1,2,*}, Marco Cintoni ³, Pauline Raoul ², Loris Riccardo Lopetuso ^{2,4}, Franco Scalfarelli ^{2,4}, Gabriele Pulcini ³, Giacinto Abele Donato Miggiano ^{1,2}, Antonio Gasbarrini ^{2,4} and Maria Cristina Mele ^{1,2}

¹ UOC di Nutrizione Clinica, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome.

Several studies have compared the gut microbiota of omnivores, vegetarians, and vegan individuals. Some of them showed higher ratios of *Bacteroides/Prevotella*, *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme*, *Klebsiella pneumoniae*, and *Faecalibacterium prausnitzii* and lower ratios of *Clostridium* cluster XIVa and *Bilophila wadsworthia* in vegetarians and vegans compared to omnivores.

Keywords: non-communicable diseases; leaky gut; gut microbiota modulation; diet; macronutrients; micronutrients; salt; food additives; low-calorie sweeteners; dietary emulsifiers; dietary habits; personalized medicine

1. Introduction

The human gastrointestinal (GI) tract harbors more than 100,000 billion microorganisms, representing 10–100 times the number of human cells [1]. Bacteria are classified according to phyla, classes, orders, families, genera, and species. Only a few phyla are represented in the gut, accounting for more than 160 species [2]. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and



Review

Food Components and Dietary Habits: Keys for a Healthy Gut Microbiota Composition

Emanuele Rinninella ^{1,2,*}, Marco Cintoni ³, Pauline Raoul ², Loris Riccardo Lopetuso ^{2,4}, Franco Scaldaferri ^{2,4}, Gabriele Pulcini ³, Giacinto Abele Donato Miggiano ^{1,2}, Antonio Gasbarrini ^{2,4} and Maria Cristina Mele ^{1,2}

¹ UOC di Nutrizione Clinica, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy; giacintoabeledonato.miggiano@policlinicogemelli.it (G.A.D.M.); mariacristina.mele@unicatt.it (M.C.M.)

Both vegans and vegetarians had lower counts of *Bifidobacterium* and *Bacteroides* species, but the quantification of fecal SCFA levels and methane production by breath revealed no difference between vegans and omnivores, demonstrating that vegan and vegetarian diets could decrease gut microbiota diversity but not decrease SCFAs and methane levels.

the optimal diet for a healthy modulation of gut microbiota.

Keywords: non-communicable diseases; leaky gut; gut microbiota modulation; diet; macronutrients; micronutrients; salt; food additives; low-calorie sweeteners; dietary emulsifiers; dietary habits; personalized medicine

1. Introduction

The human gastrointestinal (GI) tract harbors more than 100,000 billion microorganisms, representing 10–100 times the number of human cells [1]. Bacteria are classified according to phyla, classes, orders, families, genera, and species. Only a few phyla are represented in the gut, accounting for more than 160 species [2]. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and



Review

Food Components and Dietary Habits: Keys for a Healthy Gut Microbiota Composition

Emanuele Rinninella ^{1,2,*}, Marco Cintoni ³, Pauline Raoul ², Loris Riccardo Lopetuso ^{2,4}, Franco Scaldaferri ^{2,4}, Gabriele Pulcini ³, Giacinto Abele Donato Miggiano ^{1,2}, Antonio Gasbarrini ^{2,4} and Maria Cristina Mele ^{1,2}

- ¹ UOC di Nutrizione Clinica, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy; giacintoabeledonato.miggiano@policlinicogemelli.it (G.A.D.M.); mariacristina.mele@unicatt.it (M.C.M.)
- ² Istituto di Patologia Speciale Medica, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy; pauline.raoul1@gmail.com (P.R.); lopetusoloris@libero.it (L.R.L.); francoscaldaferri@gmail.com (F.S.); antonio.gasbarrini@unicatt.it (A.G.)
- ³ ...

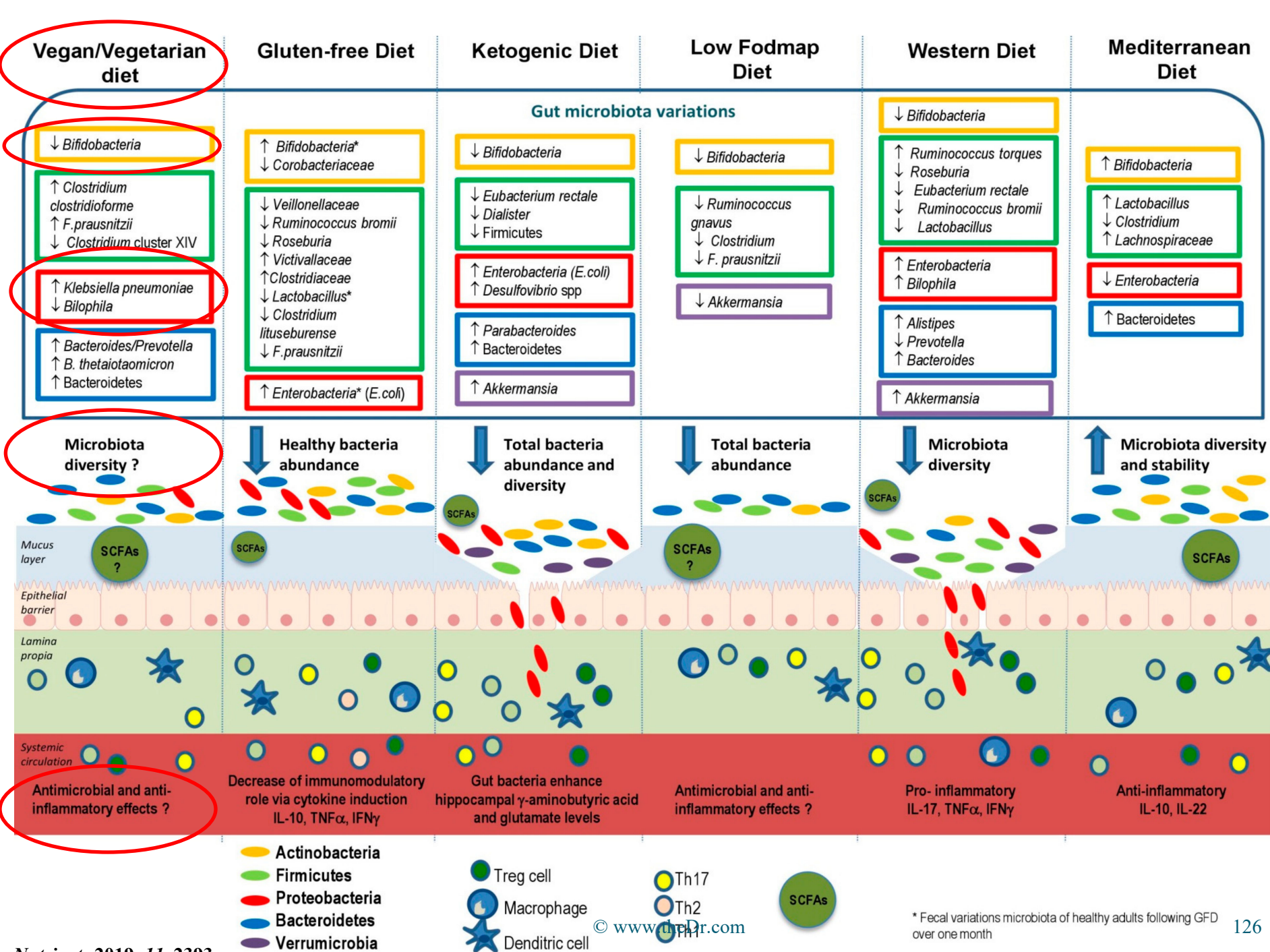
The effects of polyphenols, which are abundant in plant foods and thus in vegan and vegetarian diets, on gut microbiota modulation should be considered. Indeed, these components increase the abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*.

on the impact of single food components (macronutrients and micronutrients), salt, food additives, and different dietary habits (i.e., vegan and vegetarian, gluten-free, ketogenic, high sugar, low FODMAP, Western-type, and Mediterranean diets) on gut microbiota composition in order to define the optimal diet for a healthy modulation of gut microbiota.

Keywords: non-communicable diseases; leaky gut; gut microbiota modulation; diet; macronutrients; micronutrients; salt; food additives; low-calorie sweeteners; dietary emulsifiers; dietary habits; personalized medicine

1. Introduction

The human gastrointestinal (GI) tract harbors more than 100,000 billion microorganisms, representing 10–100 times the number of human cells [1]. Bacteria are classified according to phyla, classes, orders, families, genera, and species. Only a few phyla are represented in the gut, accounting for more than 160 species [2]. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and



* Fecal variations microbiota of healthy adults following GFD over one month

Low-FODMAP Diet



Review

Food Components and Dietary Habits: Keys for a Healthy Gut Microbiota Composition

Emanuele Rinninella ^{1,2,*}, Marco Cintoni ³, Pauline Raoul ², Loris Riccardo Lopetuso ^{2,4}, Franco Scaldaferrì ^{2,4}, Gabriele Pulcini ³, Giacinto Abele Donato Miggiano ^{1,2}, Antonio Gasbarrini ^{2,4} and Maria Cristina Mele ^{1,2}

- ¹ UOC di Nutrizione Clinica, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy; giacintoabeledonato.miggiano@policlinicogemelli.it (G.A.D.M.); mariacristina.mele@unicatt.it (M.C.M.)
- ² Istituto di Patologia Speciale Medica, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy; pauline.raoul1@gmail.com (P.R.); lopetusoloris@libero.it (L.R.L.); francoscaldaferrì@gmail.com (F.S.); antonio.gasbarrini@unicatt.it (A.G.)
- ³ Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Via Montpellier 1, 00133 Rome, Italy; marco.cintoni@gmail.com (M.C.); gabrielepulcini.med@gmail.com (G.P.)
- ⁴ UOC di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS,

A low-FODMAP diet could lead to a reduction of potential prebiotics (FOSs and GOSs), thus leading to a reduction in beneficial bacteria and fermentative effects.

structural and behavioral changes in gut microbiota. In this context, novel dietary strategies are emerging to prevent diseases and maintain health. However, the consequences of these different diets on gut microbiota modulation are still largely unknown, and could potentially lead to alterations of gut microbiota, intestinal barrier, and the immune system. The present review aimed to focus on the impact of single food components (macronutrients and micronutrients), salt, food additives, and different dietary habits (i.e., vegan and vegetarian, gluten-free, ketogenic, high sugar, low FODMAP, Western-type, and Mediterranean diets) on gut microbiota composition in order to define the optimal diet for a healthy modulation of gut microbiota.

Keywords: non-communicable diseases; leaky gut; gut microbiota modulation; diet; macronutrients; micronutrients; salt; food additives; low-calorie sweeteners; dietary emulsifiers; dietary habits; personalized medicine

1. Introduction

The human gastrointestinal (GI) tract harbors more than 100,000 billion microorganisms, representing 10–100 times the number of human cells [1]. Bacteria are classified according to phyla, classes, orders, families, genera, and species. Only a few phyla are represented in the gut, accounting for more than 160 species [2]. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and

Review

Food Components and Dietary Habits: Keys for a Healthy Gut Microbiota Composition

Emanuele Rinninella ^{1,2,*}, Marco Cintoni ³, Pauline Raoul ², Loris Riccardo Lopetuso ^{2,4}, Franco Scaldaferrì ^{2,4}, Gabriele Pulcini ³, Giacinto Abele Donato Miggiano ^{1,2}, Antonio Gasbarrini ^{2,4} and Maria Cristina Mele ^{1,2}

- ¹ UOC di Nutrizione Clinica, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy; giacintoabeledonato.miggiano@policlinicogemelli.it (G.A.D.M.); mariacristina.mele@unicatt.it (M.C.M.)
- ² Istituto di Patologia Speciale Medica, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy; pauline.raoul1@gmail.com (P.R.); lopetusoloris@libero.it (L.R.L.); francoscaldaferrì@gmail.com (F.S.); antonio.gasbarrini@unicatt.it (A.G.)
- ³ Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Via Montpellier 1, 00133 Rome, Italy; marco.cintoni@gmail.com (M.C.); gabrielepulcini.med@gmail.com (G.P.)
- ⁴ UOC di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS,

In IBS patients on a low-FODMAP diet, similar SCFA concentrations with a reduction of total bacterial abundance to 47% compared with a habitual diet.

structural and behavioral changes in gut microbiota. In this context, novel dietary strategies are emerging to prevent diseases and maintain health. However, the consequences of these different diets on gut microbiota modulation are still largely unknown, and could potentially lead to alterations of gut microbiota, intestinal barrier, and the immune system. The present review aimed to focus on the impact of single food components (macronutrients and micronutrients), salt, food additives, and different dietary habits (i.e., vegan and vegetarian, gluten-free, ketogenic, high sugar, low FODMAP, Western-type, and Mediterranean diets) on gut microbiota composition in order to define the optimal diet for a healthy modulation of gut microbiota.

Keywords: non-communicable diseases; leaky gut; gut microbiota modulation; diet; macronutrients; micronutrients; salt; food additives; low-calorie sweeteners; dietary emulsifiers; dietary habits; personalized medicine

1. Introduction

The human gastrointestinal (GI) tract harbors more than 100,000 billion microorganisms, representing 10–100 times the number of human cells [1]. Bacteria are classified according to phyla, classes, orders, families, genera, and species. Only a few phyla are represented in the gut, accounting for more than 160 species [2]. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and



Review

Food Components and Dietary Habits: Keys for a Healthy Gut Microbiota Composition

Emanuele Rinninella ^{1,2,*}, Marco Cintoni ³, Pauline Raoul ², Loris Riccardo Lopetuso ^{2,4}, Franco Scaldaferrì ^{2,4}, Gabriele Pulcini ³, Giacinto Abele Donato Miggiano ^{1,2}, Antonio Gasbarrini ^{2,4} and Maria Cristina Mele ^{1,2}

¹ UOC di Nutrizione Clinica, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy; giacintoabeledonato.miggiano@policlinicogemelli.it (G.A.D.M.); mariacristina.mele@unicatt.it (M.C.M.)

² Istituto di Patologia Speciale Medica, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy; pauline.raoul1@gmail.com (P.R.); lopetusoloris@libero.it (L.R.L.); francoscaldaferrì@gmail.com (F.S.); antonio.gasbarrini@unicatt.it (A.G.)

³ Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Via Montpellier 1, 00133 Rome, Italy; marco.cintoni@gmail.com (M.C.); gabrielepulcini.med@gmail.com (G.P.)

⁴ UOC di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Gastroenterologiche, Endocrino-Metaboliche e Nefro-Urologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS,

The integration of a low-FODMAP diet with probiotics seems to counteract gut microbiota imbalances and, in particular, restore *Bifidobacterium* levels.

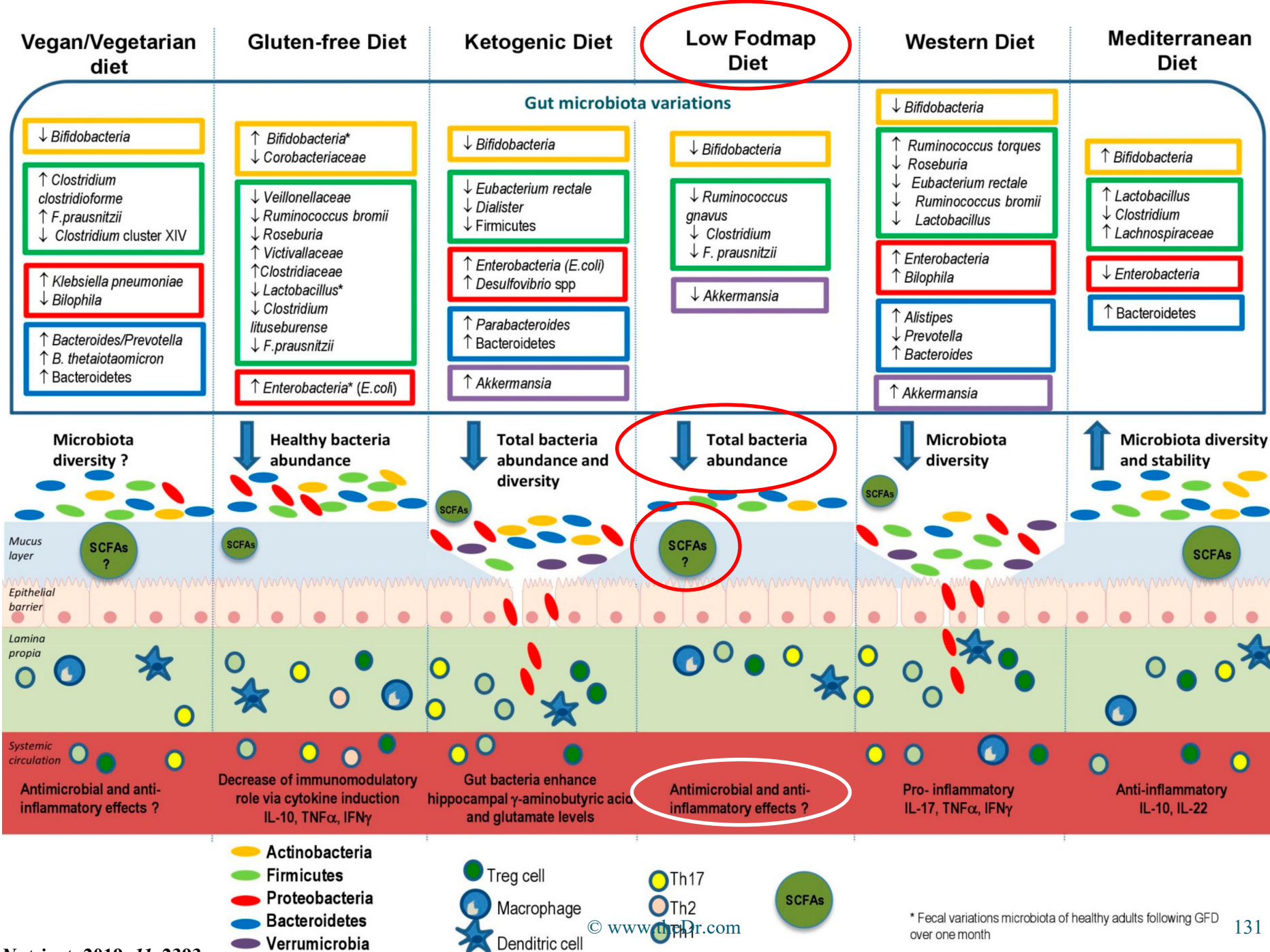
structural and behavioral changes in gut microbiota. In this context, novel dietary strategies are emerging to prevent diseases and maintain health. However, the consequences of these different diets on gut microbiota modulation are still largely unknown, and could potentially lead to alterations of gut microbiota, intestinal barrier, and the immune system. The present review aimed to focus on the impact of single food components (macronutrients and micronutrients), salt, food additives, and different dietary habits (i.e., vegan and vegetarian, gluten-free, ketogenic, high sugar, low FODMAP, Western-type, and Mediterranean diets) on gut microbiota composition in order to define the optimal diet for a healthy modulation of gut microbiota.

Keywords: non-communicable diseases; leaky gut; gut microbiota modulation; diet; macronutrients; micronutrients; salt; food additives; low-calorie sweeteners; dietary emulsifiers; dietary habits; personalized medicine

1. Introduction

The human gastrointestinal (GI) tract harbors more than 100,000 billion microorganisms, representing 10–100 times the number of human cells [1]. Bacteria are classified according to phyla, classes, orders, families, genera, and species. Only a few phyla are represented in the gut, accounting for more than 160 species [2]. The dominant gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with the two phyla Firmicutes and





Gluten Free Diet





Mediterranean Gluten-Free Diet: Is It a Fair Bet for the Treatment of Gluten-Related Disorders?

Karla A. Bascuñán^{1,2}, Luca Elli^{1,3}, Maurizio Vecchi^{3,4}, Alice Scricciolo¹, Federica Mascaretti¹, Maria Parisi¹, Luisa Doneda⁵, Vincenza Lombardo¹, Magdalena Araya⁶ and Leda Roncoroni^{1,5*}

¹ Center for Prevention and Diagnosis of Celiac Disease, Gastroenterology and Endoscopy Unit, Fondazione Istituto di Ricovero e Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, ² Department of Nutrition, School of Medicine, University of Chile, Santiago, Chile, ³ Department of Pathophysiology and Transplantation, University of

Unless education and training are provided to the patient with CD, NCGS, and Wheat Allergy, his/her choice will include a proportion of unhealthy foods, and additional health risks will be added

Giuseppe Nardone,
University of Florence, Italy
Lorenzo Norsa,
Ospedale Papa Giovanni XXIII, Italy

*Correspondence:
Leda Roncoroni
leda.roncoroni@unimi.it

Specialty section:
This article was submitted to
Nutritional Immunology,
a section of the journal
Frontiers in Nutrition

Received: 16 July 2020

Accepted: 04 November 2020

Published: 02 December 2020

Citation:
Bascuñán KA, Elli L, Vecchi M,
Scricciolo A, Mascaretti F, Parisi M,
Doneda L, Lombardo V, Araya M and
Roncoroni L (2020) Mediterranean
Gluten-Free Diet: Is It a Fair Bet for the
Treatment of Gluten-Related
Disorders? *Front. Nutr.* 7:583981.
doi: 10.3389/fnut.2020.583981

of the current knowledge about Celiac Disease (CD) and NCGS, their characteristics and central food components. Based on the Mediterranean diet pyramid developed by the Italian pediatric society, we propose a combination between the MedD and the GFD, an attractive alternative to reach a gluten-free state that at the same time is healthy, with a clear benefit to those who practice it.

Keywords: gluten-free diet, Mediterranean diet, food pyramid, cereals, pseudocereals

INTRODUCTION

Gluten related disorders share in common that they are triggered by gluten ingestion. They are a changing group of conditions, including celiac disease (CD), wheat allergy (WA), and non-celiac gluten sensitivity (NCGS) (1). Although mediated by different pathogenic pathways, their clinical manifestations may be similar (2), posing difficulties at the time of diagnosis (3). Their only effective treatment is a gluten-free diet (GFD), which eliminates wheat, rye, and barley consumption. GFD consists of a combination of naturally gluten-free foods (GFF) and gluten-free substitutes prepared with a variety of gluten-free foods and cereals (4). Although highly effective, GFD requires supervision by a trained professional, who must educate the patient and manage the diet, because this is often poor in fiber and vitamins and high in lipid and sugar content (5). In fact, excessive weight and obesity can also be a concern in celiac patients following a GFD, due to the rich-energy gluten-free foods/products commonly eaten (6). Currently available gluten-free products are often low in protein, with high fat and salt content. Higher levels of dietary fiber



Letter to the Editor

Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects – comment by Jackson

A paper in the *British Journal of Nutrition* by De Palma

Frank W. Jackson

Wheat (78 %) and barley (3 %) together provide 81% of oligofructose and inulin (prebiotics) for average North Americans, with onions giving 10 %

Loos *et al.*⁽⁴⁾ reported that wheat (78%) and barley (3%) together provide 81 % of oligofructose and inulin for average North Americans, with onions giving 10%. Moshfegh *et al.*⁽⁵⁾ found that, in Americans, wheat supplied 70% of these two fructans, with onions contributing 25%. Thus, it appears that a GFD in both coeliac and non-coeliac subjects could produce similar, potentially adverse, changes in the microbiota solely on the basis of a marked reduction in intake of naturally occurring fructans which have prebiotic action. Provision of gluten-free but prebiotic-rich foods and/or a supplement of fructan-type prebiotics could avoid this situation and, in so doing, provide important support to the intestinal microbiota as well as important nutritional guidance for the coeliac patient.

F. W. J. is the president of Jackson GI Medical which markets a prebiotic supplement.

References

1. De Palma G, Nadal I, Collado MC, *et al.* (2009) Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Br J Nutr* **102**, 1154–1160.
2. Collado M, Calabuig M & Sanz Y (2007) Differences between the faecal microbiota of coeliac infants and healthy controls. *Curr Issues Intest Microbiol* **8**, 9–14.
3. Gibson GR (2008) Prebiotics as gut microflora management tools. *J Clin Gastroenterol* **42**, Suppl. 2, S75–S79.
4. Van Loos J, Coussement P, De Leenheer L, *et al.* (1995) On the presence of inulin and oligofructose as natural ingredients in the Western diet. *Crit Rev Food Sci Nutr* **35**, 525–552.
5. Moshfegh AJ, Friday JE, Goldman JP, *et al.* (1999) Presence of inulin and oligofructose in the diets of Americans. *J Nutr* **129**, 1407S–1411S.



Accumulation of Heavy Metals in People on a Gluten-Free Diet



Stephanie L. Raehsler,* Rok Seon Choung,* Eric V. Marietta,*^{†,§} and Joseph A. Murray*[§]

^{*}Division of Gastroenterology and Hepatology, [†]Department of Dermatology, [§]Department of Immunology, Mayo Clinic, Rochester, Minnesota

BACKGROUND & AIMS:

Specific foods such as fish and rice have high concentrations of metals such as arsenic, mercury, lead, cadmium, and cobalt. Many gluten-free diets (GFDs) include these foods, so we evaluated whether a GFD was associated with increased metal bioaccumulation.

METHODS:

We performed a population-based, cross-sectional study using data collected from the National Health and Nutrition Examination Survey (NHANES), from 2009 through 2012, collecting information on the diagnosis of celiac disease and adherence to a GFD. We tested NHANES blood samples to identify individuals with undiagnosed celiac disease, using assays for immunoglobulin A tissue transglutaminase followed by a confirmatory test for endomysial antibody. Among a total of 11,354 NHANES participants, celiac disease was diagnosed in 55 participants, based on test results or a reported clinical diagnosis. We collected NHANES survey data on blood levels of lead, mercury, and cadmium from subjects who were on a GFD (n = 115) and

Gluten-containing cereals are one of the major sources of dietary fiber in the United States, so people following a GFD may be at risk for inadequate fiber intake

urine samples from subjects not on a GFD (8.38 mcg/L) ($P = .002$). After controlling for demographic characteristics, levels of all heavy metals remained significantly higher in persons following a GFD, compared with those not following a GFD. After exclusion of persons with celiac disease, people without celiac disease on a GFD (n = 101) had significantly increased blood concentrations of total mercury (1.40 mcg/L) than persons without celiac disease and not on a GFD (n = 10,890) (0.93 mcg/L; $P = .02$) and higher blood concentrations of lead (1.44 vs 1.13 mcg/L; $P = .01$) and higher urine concentrations of total arsenic (14.69 mcg/L [n = 3632] vs 8.32 mcg/L [n = 28]; $P = .01$). Blood samples from persons without celiac disease avoiding gluten had higher levels of cadmium (0.42 mcg/L) than persons without celiac disease and not following a GFD (0.34 mcg/L), but this difference was not significant ($P = .06$).

CONCLUSIONS:

In an analysis of data collected from NHANES, persons on a GFD had significantly higher urine levels of total arsenic and blood levels of mercury, lead, and cadmium than persons not avoiding gluten. Studies are needed to determine the long-term effects of accumulation of these elements in persons on a GFD.

Keywords: Heavy Metals; Bioaccumulation of Metals; Celiac Disease; Gluten-Free Diet.

Abbreviations used in this paper: CD, celiac disease; CI, confidence interval; EMA, endomysial antibody; GFD, gluten-free diet; NHANES, National Health and Nutrition Examination Survey; OSHA, Occupational Safety and Health Administration; ITG, tissue transglutaminase.

Most current article

© 2018 by the AGA Institute
1542-3565/\$36.00

<http://dx.doi.org/10.1016/j.cgh.2017.01.034>



Effects of a gluten-free diet on gut microbiota and immune function in healthy adult humans

Yolanda Sanz

Microbial Ecophysiology and Nutrition Group; Institute of Agrochemistry and Food Technology (IATA); Spanish National Research Council (CSIC); Valencia, Spain

Diet is a major environmental factor influencing gut microbiota diversity and functionality, which might be relevant for human health. This ecosystem is greatly influenced by the

functions, including the provision of attributes not encoded in the human genome.¹ This ecosystem is greatly influenced by the

A preliminary study was conducted to establish whether the GFD in itself could modify the composition and immune properties of the gut microbiota. The trial included 10 healthy subjects (30.3 yrs old), which were submitted to a GFD over one month.

Key words: gut microbiota; gluten-free diet; celiac disease; immunity; probiotics; polysaccharides; prebiotics

Submitted: 11/05/09

Revised: 02/03/10

Accepted: 03/16/10

Previously published online:

www.landesbioscience.com/journals/gut-microbes/article/11868

Correspondence to:

Yolanda Sanz; Email: yolsanz@iata.csic.es

Addendum to: De Palma G, Nadal I, Collado MC, Sanz Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Br J Nutr* 2009; 102:1154–60; PMID: 19445821; DOI: 10.1017/S0007114509371767.

which represent an altered microbiota, also exerted lower immune stimulatory effects on peripheral blood mononuclear cells than those of subjects on a regular gluten-containing diet. This addendum presents further discussion on the rationale behind these findings, limitations of the study and possible consequences of dietary counselling in the care process of celiac disease patients.

Relationship between the Gluten-Free Diet and the Gut Microbiota

The human intestinal tract harbors a collection of beneficial bacteria (symbionts/mutualists) that perform an array of

the adherence to a strict gluten-free diet (GFD) usually leads to the remission of the major clinical symptoms, nutritional deficiencies and health complications are often reported in treated patients.^{5,7} In addition, the microbiota of patients under a GFD is not completely restored in comparison with that of healthy subjects.⁸⁻¹⁰ In this context, we published a preliminary study to establish whether the GFD in itself could lead to modifications on the composition and immune properties of the gut microbiota.¹¹ This study included 10 healthy subjects (30.3 years-old), who were following a GFD over one month by replacing the gluten-containing foods they usually ate with certified gluten-free foods (with no more than 20 parts per million

Effects of a gluten-free diet on gut microbiota and immune function in healthy adult humans

Yolanda Sanz

Microbial Ecophysiology and Nutrition Group; Institute of Agrochemistry and Food Technology (IATA); Spanish National Research Council (CSIC); Valencia, Spain

Analysis of fecal microbiota and dietary intake indicated that:

- numbers of healthy bacteria **decreased**, (*Bifidobacterium*, *B.longum* and *Lactobacillus*),
- numbers of unhealthy bacteria **increased** (*E. coli* and total Enterobacteriaceae) parallel to reductions in the intake of polysaccharides after following the GFD,
- which represent **an altered microbiota**, favoring the overgrowth of opportunistic pathogens and weakening the host defenses against infection and chronic inflammation via possible alterations in mucosal immunity,

man subjects. Br J Nutr 2009; 102:1154-60; PMID: 19445821; DOI: 10.1017/S0007114509371767.

collection of beneficial bacteria (symbionts/mutualists) that perform an array of

usually ate with certified gluten-free foods (with no more than 20 parts per million

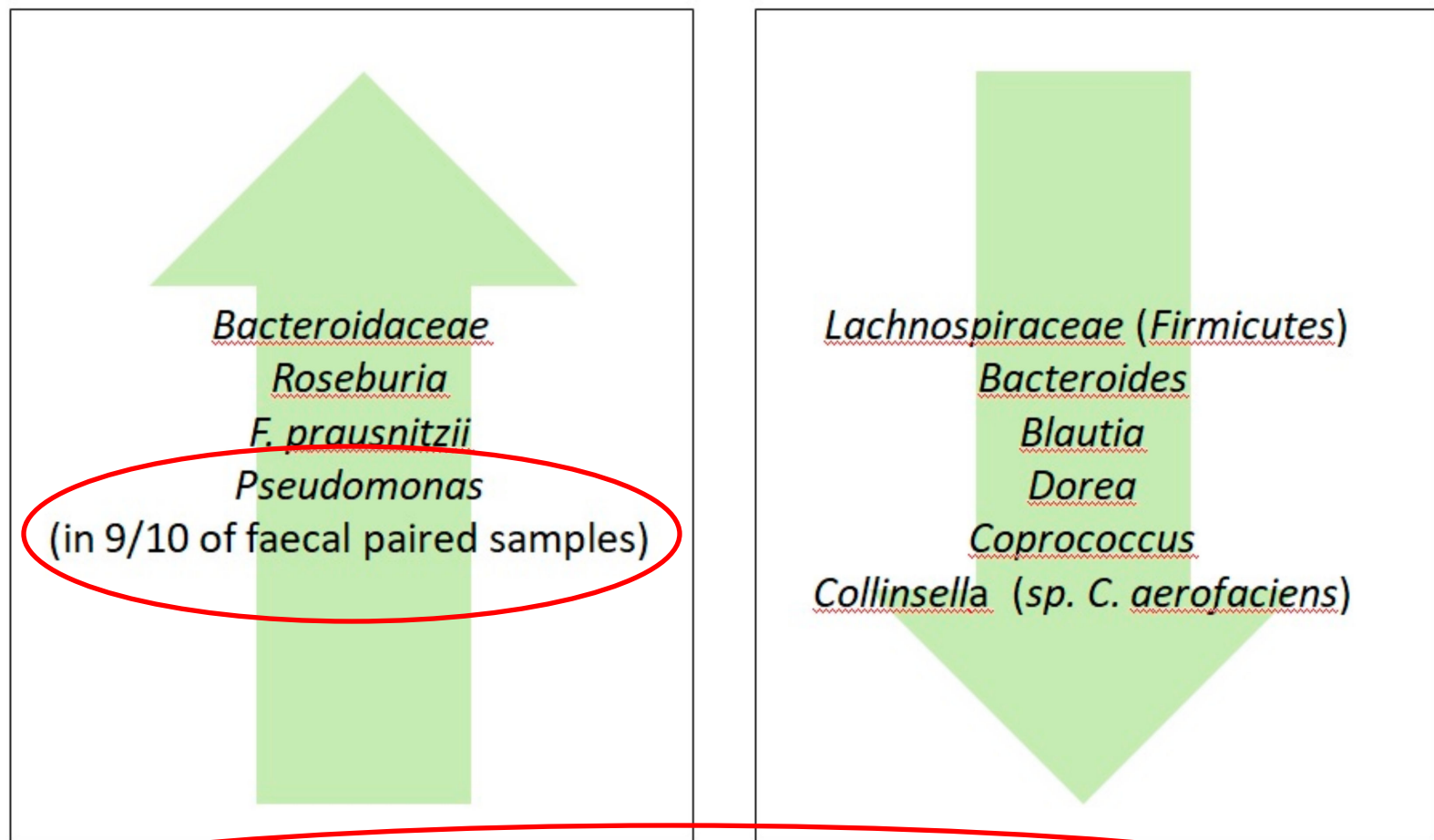
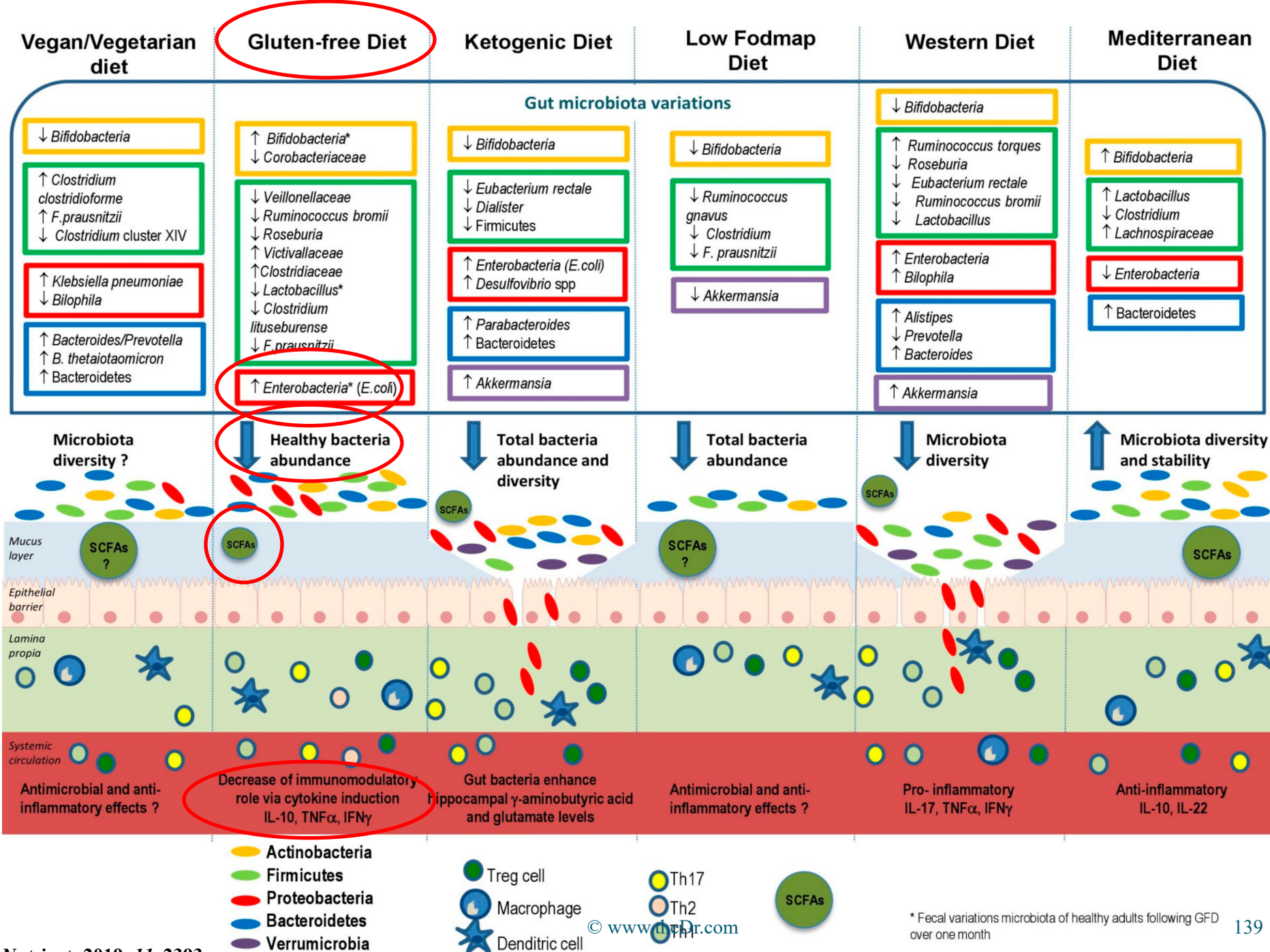


Figure 3. Effects of GFD on the abundance of bacterial populations in non-celiac gluten/wheat sensitivity (NCG/WS) patients.



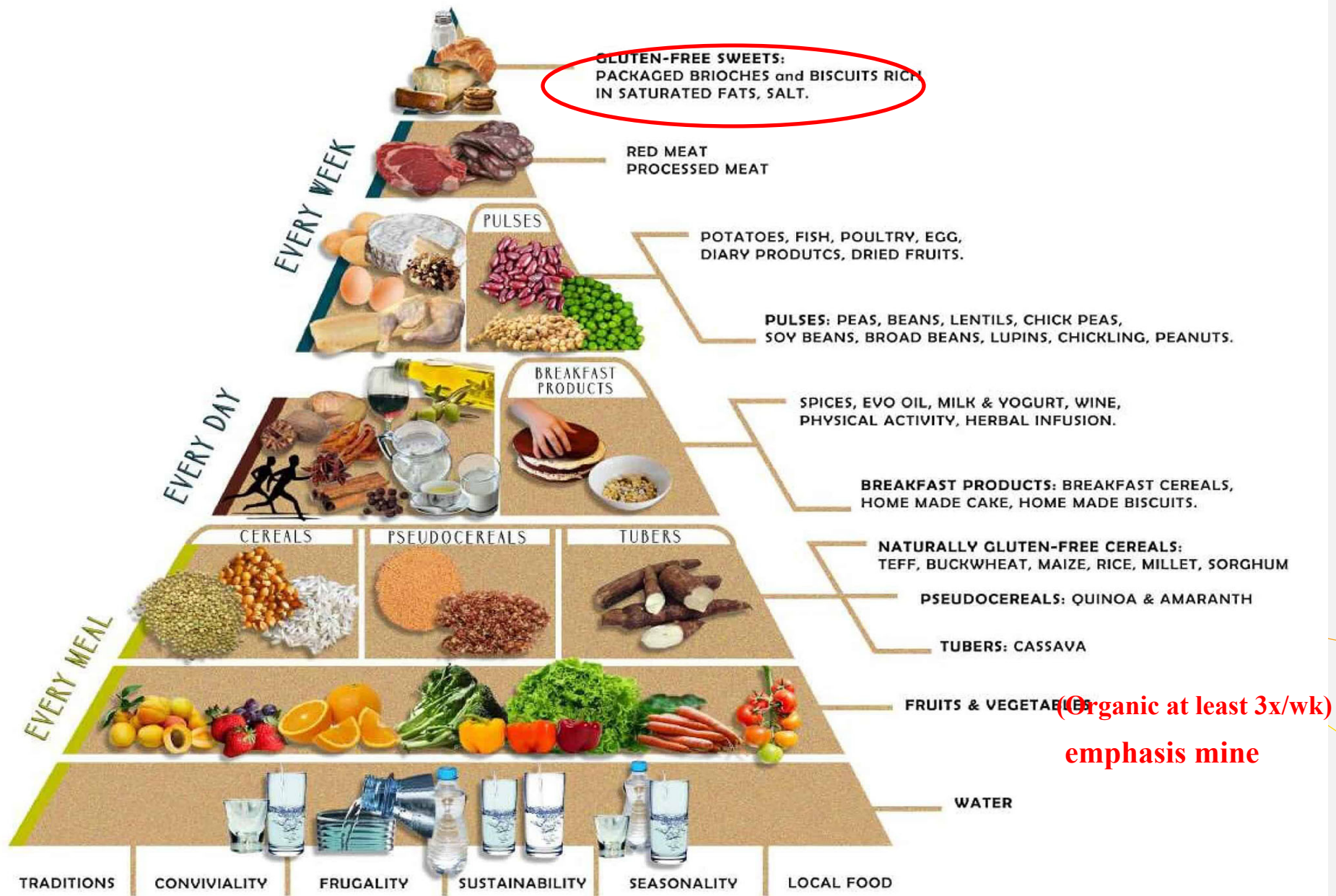


FIGURE 1 | The Mediterranean GFD pyramid: a gluten-free lifestyle. A new graphic representation of the food pyramid based on the MedD is conceived, where coexistence with the GFD is possible. The Mediterranean GFD pyramid gathers www.frontiersin.org recommendations considering lifestyle, dietary, sociocultural, environmental, and health challenges of individuals who follow a GFD in the context of healthy eating based on the MedD. MedD, Mediterranean diet; GFD, gluten-free diet.







Take Care of Yourself



Make Sure to Tell those Important to You How Much You Love them



Big Boss



“Thank You for Your Kind Attention”





Wishing you Sunrises of Beauty throughout your life