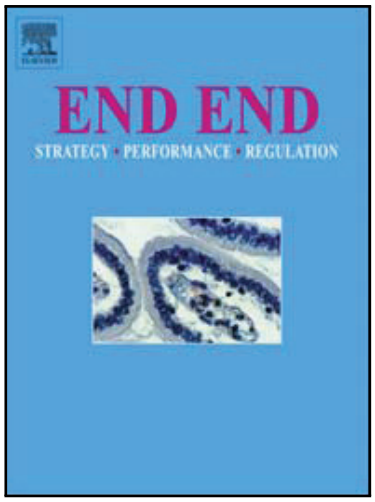
Accepted Manuscript



Applying Precision Medicine to Healthy Living for the Prevention and Treatment of Cardiovascular Disease

Ross Arena PhD , Cemal Ozemek PhD , Deepika Laddu-Patel PhD , Tavis Campbell PhD , Codie R. Rouleau PhD , Robert Standley PhD , Samantha Bond MS , Eulàlia P. Abril PhD , Andrew P Hills PhD , Carl Lavie MD

PII: S0146-2806(18)30081-1
DOI: 10.1016/j.cpcardiol.2018.06.001
Reference: YMCD 379

To appear in: *The End-to-end Journal*

Please cite this article as: Ross Arena PhD , Cemal Ozemek PhD , Deepika Laddu-Patel PhD , Tavis Campbell PhD , Codie R. Rouleau PhD , Robert Standley PhD , Samantha Bond MS , Eulàlia P. Abril PhD , Andrew P Hills PhD , Carl Lavie MD , Applying Precision Medicine to Healthy Living for the Prevention and Treatment of Cardiovascular Disease , *The End-to-end Journal* (2018), doi: 10.1016/j.cpcardiol.2018.06.001

Applying Precision Medicine to Healthy Living for the Prevention and Treatment of Cardiovascular Disease

Ross Arena, PhD[1], Cemal Ozemek, PhD[1], Deepika Laddu-Patel, PhD[1], Tavis Campbell, PhD[2], Codie R. Rouleau, PhD[1,3], Robert Standley, PhD[4], Samantha Bond, MS[1], Eulàlia P. Abril, PhD[5], Andrew P Hills, PhD[6], Carl Lavie, MD[7]

[1]Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, USA

[2]Department of Psychology University of Calgary, 2500 University Dr. N.W. Calgary, AB, T2N 1N4, Canada

[3]TotalCardiology Rehabilitation, 2225 MacLeod Trail South, Calgary, AB T2G5B6, Canada

[4]The Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA

[5]Department of Communication, College of Liberal Arts and Sciences, University of Illinois at Chicago, Chicago, IL, USA

[6]College of Health and Medicine, University of Tasmania, Launceston, TAS, Australia

[7]Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, LA, USA

Address for Correspondence
Ross Arena, PhD, PT
Department of Physical Therapy
College of Applied Health Sciences
University of Illinois at Chicago
1919 W. Taylor Street, 454 AHSB
Chicago, IL 60612
Office: 312.355.3338
raarena@uic.edu

Word count: Abstract: 236, **Text:** 7,703

Abstract

Healthy living medicine (HLM) is an emerging concept that recognizes the importance of: 1) Moving more and sitting less; 2) Consuming a healthy diet at the appropriate caloric load; 3) Maintaining a healthy body weight; and 4) Not smoking. Suffice to say, HLM should be practiced by all health professionals, prescribing a personalized healthy living polypill to individuals under their care while titrating the dosage for optimal adherence and therapeutic efficacy. Traditionally, HLM, particularly when practiced in the context of physical activity and diet, is commonly viewed as an all-or-none and one-size-fits-all paradigm. As an example, there has been a dichotomous perception to physical activity messaging, where achieving anything less than 150 minutes of moderate-intensity physical activity per day is not beneficial. The same holds true for the all-or-none perception of 5 servings of fruits and vegetables per day; anything less is not beneficial. While these are certainly desirable targets, healthy living practices at levels below current guidelines portends significant health benefits. Precision medicine is defined as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person". Much of the focus in precision medicine has been directed towards genomics and only recently has the influence of environment and lifestyle been considered. This review will highlight the importance of HLM directed toward the prevention and treatment of chronic diseases in the context of precision medicine.

Key Words: Physical activity; Healthy Nutrition; Moving more; Individualized; Weight loss; Behavioral counseling

Introduction

Healthy living medicine (HLM) is an emerging concept that recognizes the importance of: 1) Moving more and sitting less; 2) Consuming a healthy diet at the appropriate caloric load; 3) Maintaining a healthy body weight; and 4) Not smoking.[1, 2] It is now well recognized that the practice and delivery of HLM is the primary way to prevent the spectrum of chronic diseases that are currently the leading health concern globally; the incidence and prevalence of cardiovascular disease (CVD) is at the forefront of conditions that require significant attention and a paradigm shift in treatment.[3-5] Ideally, preventing CVD from ever being diagnosed should be the primary goal, which can only be achieved through the practice of HLM. Research has shown that in those individuals who emulate the ideal healthy living (HL) phenotype (i.e., achieving or exceeding guideline recommendations for exercise and diet, maintaining a healthy body weight and not smoking), the risk of developing CVD prematurely is reduced by 60% or more.[6-8] Additionally, a recent investigation found that compared to those leading an unhealthy lifestyle, individuals who emulated the ideal HL phenotype extended their life expectancy by, on average, more than 10 years.[9] In those diagnosed with a chronic disease, HLM plays an integral role in improving prognosis and quality of life while reducing health care costs.[10-13] Even for those individuals who do not have an ideal HL phenotype but decide to make some positive changes, such as exercising 2-3 times per week and/or consuming 2-3 servings of fruits and vegetables per day, risk reductions for CVD are still significant and clinically meaningful.[8] Suffice to say, HLM should be practiced by all health professionals, prescribing a personalized healthy living polypill to individuals under their care while titrating the dosage for optimal adherence and therapeutic efficacy.[1, 14] Moreover, HL should be encouraged and made easily achievable outside of the traditional health care arena. Public health messaging, communities, schools, and

workplaces all play a key role in the practice of HLM.[15] The more an individual is immersed in a culture of HL, the easier it will be to make healthier choices.

Becoming more physically active and consuming a nutritious diet are two ingredients of HLM that garner a great deal of attention, physical activity (PA) in particular. This is due to the fact that being more physically active and consuming a healthy diet portends significant benefits irrespective of an individual's health status (e.g., those who are obese, at risk for a chronic disease, diagnosed with a chronic disease, etc.).[16-19] Traditionally, HLM, when practiced in the context of physical activity and diet, is commonly viewed as an all-or-none and one-size-fits-all paradigm. As an example, there has been a dichotomous perception to physical activity messaging, where achieving anything less than 150 minutes of moderate-intensity physical activity per day is not beneficial.[20] The independent benefits of moving more and sitting less, outside of a structured exercise program, are rarely discussed or publicized.[21, 22] The same holds true for the all-or-none perception of 5 servings of fruits and vegetables per day; anything less is not beneficial.[23, 24] While these are certainly more desirable levels, participating in physical activity and consuming fruits and vegetables at levels below current guideline recommendations portend significant health benefits.[8, 22, 25, 26] Moreover, it is critical that the population at large recognizes that any type of movement/physical activity is beneficial, both recreational and non-recreational.[17] In this context, there seems to be a greater degree of flexibility in delivering HLM, allowing for a more individualized approach that has the potential to improve long-term adherence. In other words, the alignment of precision medicine and HLM is warranted.

The National Research Council provided the initial framework for the development and implementation of precision medicine in 2011,[27] and paved the way for President Obama's Precision Medicine Initiative in 2015. This initiative defines precision medicine as "an emerging

approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person". Much of the focus in precision medicine has been directed towards genomics and only recently has the influence of environment and lifestyle been considered. The addition of environmental and lifestyle factors to precision medicine are important because the wealth of randomized clinical trials (RCTs) indicating that a healthy lifestyle, characterized by daily physical activity, maintenance of normal body weight, sound psychological health, a healthy diet, and non-smoking, lowers the risk and/or prevents development of several chronic diseases, such as diabetes [28] and CVD[29]. While RCTs designed to improve healthy living provide valuable information, they are often conducted in very controlled settings outside of "real-world" settings, and the biological responses can be variable due to individual biology, behavior and environment. To improve compliance with long-term HL practices, the tenets of precision medicine should be embraced by practitioners. As illustrated in **Figure 1**, there are key treatment and supportive components when striving for precision in HLM that is directed toward improving physical activity patterns, consumption of a healthier diet, achieving/maintaining a healthy body weight and not smoking. To be optimally effective, the key ingredients of the HL polypill with respect to dosage and composition should be highly individualized. This review will highlight the importance of HLM directed toward the prevention and treatment of chronic diseases in the context of precision medicine.

Precision in Cognitive Behavioral Therapy: The Enteric Coating of the Healthy Living Polypill

Enteric coating, from a pharmacological perspective, is a polymer used to optimize the timing of drug release. In this context, mental health and cognitive behavioral therapy can be viewed as the enteric coating of the HL polypill, optimizing the release and efficacy of lifestyle

interventions; individuals who are psychologically healthy and counseled using a tailored approach and more likely to adopt HL behaviors. There are two fundamental areas in which the study of psychosocial factors can improve precision in HLM. The first involves the assimilation of information on symptoms, behavior and environment into better understanding individual health and tailoring treatment. The second encompasses understanding how patients, health care providers and policymakers interact with precision medicine approaches to improve uptake, practice and policy.

Treatment of Mental Health Conditions linked to Healthy Living and CVD

Clinically significant associations have been consistently reported between psychological distress and the major modifiable risk factors for CVD, including tobacco use, lack of PA, medication adherence and unhealthy diet.[30] In addition, several mental health concerns, including depressed mood, anxiety and hostility are independently associated with the onset and prognosis of CVD.[31-33] For example, rates of major depression are elevated in CVD patients and it is associated with greater morbidity and mortality. Symptoms of major depression predict survival post-myocardial infarction and among patients with heart failure (HF) and unstable angina, even following adjustment for traditional and non-modifiable risk factors.[34-36] In addition, a dose-response association has been reported between level of depressed mood and survival over several years.[37] A variety of interventions have been evaluated to treat depressed mood in CVD with exercise, cognitive behavioral therapy (CBT) and other psychotherapies, and anti-depressant medications all demonstrating some efficacy.[38] Although it remains equivocal whether or not improvements in depressed mood are independently associated with improved cardiovascular outcomes[30], an arguably larger concern is that the selection of treatment modality lacks empirical justification. From the list of potential talk therapy and anti-depressant

medication options, it is unclear which is best to treat both depressed mood and reduce CVD risk.[38] This may in part reflect the heterogeneity of symptom patterns and the potential underlying mechanisms inherent in a multi-faceted illness like major depressive disorder, which may include low self-esteem, loss of interest in normally enjoyable activities, low energy, pain without a clear cause, changes in sleep and weight. Precision medicine holds promise for improving outcomes by selecting treatment based on bio-behavioral characteristics of symptom clusters. In support of this notion, Dunlop and colleagues [39] used functional MRI resting-state functional connectivity analyses in 122 depressed patients randomly assigned to 12 weeks of either CBT or antidepressant medication. Connectivity analyses using a bilateral subcallosal cingulate cortex (SCC) seed demonstrated that resting-state functional connectivity with the SCC and three areas (the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex) was differentially associated with outcomes of remission and treatment failure to CBT and antidepressant medication. Depressed patients who responded to CBT tended to demonstrate stronger patterns of connectivity between frontal areas of the brain (e.g., those involved in speaking, planning, and problem solving) with other areas of the brain, while those with lower connectivity responded best to anti-depressant medication. While promising, this approach has yielded inconsistent findings in similar investigations[40] and future research using resting-state functional connectivity and other methods identifying depression subtypes is needed to elaborate this preliminary work and extend it to patients with or at risk of CVD. Ultimately, a better understanding of potential pathophysiological mechanisms associated with both depressed mood and CVD will help to determine the best management strategies.

Challenges of Implementing Precision medicine for the Patient / Provider Interaction

Despite consistent and convincing evidence of clinically meaningful health improvements associated with HL behaviors, in combination with large-scale efforts at promoting health behaviors for the prevention and treatment of CVD, rates of adherence to chronic disease treatment regimens are typically reported to be between 30 to 50%.[41] This modest success of public health and individual efforts to improve risk factors like lack of PA and impoverished diet in order to prevent and treat CVD persists despite widespread improvements in public literacy concerning the benefits of a healthy lifestyle.[42] This may in part reflect the phenomenon of information being necessary but insufficient to motivate health behavior change. For example, it is unlikely that current smokers are unaware of potential health risks but persist in the behaviour due to addiction and a variety of perceived benefits. Simply informing patients that they should adopt a particular exercise regimen based on their individual profile and why this can be beneficial is typically ineffective at eliciting successful long-term behavior change.[43] More sophisticated theory-based health behavior change efforts have been met with greater success. For example, the Diabetes Prevention Program, which used a variety of well-established behavior change strategies derived from the social sciences to promote exercise and healthy diet, was associated with a decreased risk of pre-diabetes progressing to diabetes for several years.[44] In the context of precision in HLM, inadequate adherence and persistence will remain an important challenge. For example, despite clear communication to a patient that a particular behavioural health prescription might be ideal, their individual *preferences* might trump acceptance and there is nothing inherent in the precision medicine approach to address this issue. Further, health literacy becomes a greater challenge for adherence with precision medicine given the lack of ability to convey simple and harmonized public health messaging. Finally, precision medicine will not only provide information regarding who is likely to benefit from a HL

intervention, it will also identify who will not respond to treatment, resulting in the potential for patient disillusionment and disengagement with the treatment process. With respect to health care provider adherence with precision medicine prescriptions for HL, there is also a potential for clinical inertia, commonly defined as the failure to initiate or intensify therapy, or a failure to follow clinical practice guidelines.[45] Reasons include the added complexity of synthesizing all of the information inherent in not prescribing a one-size-fits-all approach, as well as the difficulty in communicating individualized courses of treatment to patients.[46] Combined, both patient and provider challenges in successfully implementing precision in HLM into routine care highlight the need for the use of evidence-based health behavior change interventions to be integral to the process. For example, Motivational communication (MC) represents a coherent set of strategies that have demonstrated efficacy for improving adherence to a range of behavioral health interventions.[47-49] MC includes evidence-based, patient-centered techniques designed to promote motivation for behavior change, including cognitive-behavioral strategies [50], motivational interviewing[51], and/or interventions based on well-established theories of motivation (e.g., self-determination theory [52], social-cognitive theory [53], theory of planned behavior[54], and the transtheoretical model[55]. There is a precedent for this approach with evidence-based guidelines from the U.K. [National Institute for Health and Care Excellence (NICE)] including descriptions of how health behavior change interventions can be incorporated as part of standard care.[56] Future work is needed to establish what constitutes competently delivered health behavior change interventions in precision medicine to improve patient health outcomes.

Precision in Healthy Living Medicine: The Key Polypill Ingredients

Precision for Physical Activity and Moving more

Adopting a physically active lifestyle as a primordial or secondary preventative approach to combating chronic diseases has been a cornerstone recommendation endorsed across numerous health organizations.[57-62] Increasing PA is also known to improve cardiorespiratory fitness (CRF), an independent predictor of CVD and all-cause mortality.[63-67] Although PA interventions in sedentary populations lead to group increases in CRF, it is apparent that CRF responses to PA are not uniform across all individuals. Seminal findings from the HERITAGE family study provided robust evidence identifying a wide range (0 to over 50%) of CRF responses to a standard 20-week PA intervention.[68] Further examination of familial responses to PA identified that 47% of the gains in fitness were attributable to heritability.[68] Recent trials have corroborated these observations, highlighting that uniform PA recommendations to increase CRF may not apply for a large proportion of the population.[69] Moreover, individuals already diagnosed with CVD who don't respond to an exercise intervention (i.e., improve CRF) demonstrate a worse prognosis compared to those individuals who do respond.[70, 71] These findings collective support a personalized, precision approach to PA interventions, one that focusses on eliciting as high of a CRF response as possible.

In recent years, the notion that accumulating the recommended weekly PA volume of either 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity would lead to equivalent outcomes has been contested.[72] A growing body of evidence demonstrates that at fixed exercise volumes, higher exercise intensities are associated with greater improvements in CRF and other cardio metabolic risk factors. Ross and colleagues[69] randomized sedentary, middle-aged, men and women to perform PA at a: 1) low-amount - low-intensity (~30 minutes at 50% CRF); 2) high-amount - low-intensity (~60 minutes at 50% CRF); or 3) high-amount - high-intensity (~40 minutes at 75% CRF) PA 5 days per week for 24 weeks. By assessing CRF

at 4, 8, 16, and 24 weeks, the authors found that the number of non-responders to the respective PA interventions gradually decreased at each time point. However, at the end of the intervention, 38.5% (15 of 39) of the low-amount - low-intensity cohort, 17.6% (9 of 51) high-amount - low-intensity cohort, and 0% (0 of 31) of the high-amount - high-intensity cohort remained non-responsive to the intervention. The authors concluded that increasing the amount and/or intensity of exercise significantly reduces or possibly abolishes the number of non-responders in a sedentary cohort. This suggests that the precision of PA prescriptions to promote gains in CRF may be enhanced by increasing intensity in non-responders to moderate-intensity PA. Future studies are needed to confirm this by identifying non-responders and increasing PA quantity and/or intensity.

Although CRF has been established as a highly predictive metric for future CVD and all-cause mortality, protective health effects may still be acquired by engaging in regular PA despite the absence of improvements in CRF. Similar decreases in abdominal obesity, body weight, and enhanced glucose tolerance were noted by Ross et al.[73] among PA intervention groups (low-amount - low-intensity; high-amount - low-intensity; and high-amount - high-intensity PA) and were found to be independent of changes in CRF. These findings highlight the importance of a paradigm shift in PA promotion and counseling, one that encourages individuals to move more and sit less. In addition to the benefits of participation in a structured exercise program, decreasing sitting time and taking more steps in a day also portend independent health benefits.[74, 75] Evidence indicates that individuals who are at a low level of PA in their daily lives are not aware of the benefits of moving more in general, reporting a narrow view of what types of PA portend health benefits (i.e., only vigorous PA).[76] Such a narrow view of the types of movement that are beneficial to one's health may be a barrier (i.e., perception that the level of PA needed

for health benefits is not attainable) to those who would benefit most – individuals who are currently sedentary.

While the general recommendation of becoming physically active should be endorsed to all individuals for overall health, future efforts will be needed to identify the specific quantity and intensity of PA needed to improve cardiometabolic risk factors. A greater understanding of the specific doses of PA required for accumulating health benefits will add to the level of precision practitioners prescribe structured exercise programs and overall PA recommendations to combat CVD. Given the current state of evidence, all individuals should be encouraged to move more every day; sit less, take more steps and ideally participate in a regular exercise program.[74] We must also consider an individual's motivations and perceptions with respect to moving more and participating in a regular exercise program.[76, 77] The more a movement plan is individualized to align with a person's motivations and interests while working to overcome barriers, both real and perceived, the more likely they will adopt and adhere to a more physically active lifestyle.

Precision for Nutrition

Current national and global dietary recommendations are founded on nutrient-specific reference values developed in efforts to prevent deficiency-related and major chronic disease.[78] While at best, nutrition guidelines are generalizable to populations, an inherent limitation of this "one-size-fits-all" approach is that guidelines do not account for the variable factors between individuals (e.g., sex/gender, ethnicity, cultural preferences, life stage, health status, physical activity, etc.) that differentiate nutrition requirements, doses and responses to nutrients. In efforts to address gaps in current treatment approaches, "precision nutrition," has surfaced in the scientific and public health community, heralding pro-active, individualized dietary strategies to

promote optimal health and improve overall health trajectory of individuals. The impetus for a personalized nutrition agenda has emerged as a strategy to address inter-individual variability responses to dietary intervention recognizing that individual phenotypic responses are presumably modulated by environment (i.e., diet), biology, and genetics.[78-80] Thus, a critical pursuit of the precision nutrition initiative has been to develop comprehensive and dynamic nutritional recommendations that take into account the diversity of an individual, as well as the multifactorial and continuously evolving environment to optimize overall health trajectory. Precision nutrition strategies therefore reflect a clear divergence from standardized public health nutrition practices in that they *not only* deliver customized nutrition recommendations but also utilize tailored dietary assessment methods to better inform treatment strategies and refine disease prevention and risk stratification.[81-83] Below we discuss how the "bottom's up approach" applied in precision nutrition, which specifically integrates genetics and various omics platforms with nutrition and dietary characteristics, has led to recent advances in identifying an individual's 'nutritional phenotype'[84] and how this translates to metabolic disease risk.

Propelled by advances made in human genome sequencing and genetic technologies, 'nutri*genomics*' and 'nutri*genetics*' have since emerged as part of the precision nutrition efforts to better understand the overall impact nutrition has on genes, and subsequently the effect that genetic variation has on an individual's response to nutrition interventions.[78] Although inherently different, nutrigenomics and nutrigenomics represent promising opportunities to deliver a "menu" of nutritional requirements that are customized to an individual based on their inherited and acquired genetic background, and changes in genetic characteristics that occur depending on life stage, lifestyle, environment, or in response to dietary preferences and health status.[78] In this regard, there have been a number of advances and adoptions made in high-throughput "omic"

technologies enabling researchers to exploit individual genetic and genomic information, and thus provide a more comprehensive evaluation of specific gene-nutrient or gene-nutriome (i.e., combination of nutrients) interactions that may potentially modulate disease susceptibility.[78, 85] Metabolomics, for example, presents a rapidly growing area of precision nutrition, emerging as a natural consequence to better understand the inter-individual diversity in the metabolic response to the same foods, and whether certain food-derived biomarkers (referred to as metabolites) act as mediators, or are causal in the biological pathways that link diet to disease. In essence, metabolomics provide the metabolic "blueprint" of the food and nutrients an individual consumes relative to their whole meal[86] or diet pattern.[87, 88] To illustrate this concept, Flogel and colleagues recently identified a network of metabolites known to play a role in fatty acid and carbohydrate metabolism. Further analysis by investigators revealed inverse associations between both metabolite networks and whole grain consumption, but positive associations with obesity, suggesting a mechanistic explanation as to how refined carbohydrates may contribute to the development of impaired glucose metabolism and insulin resistance, and increased oxidative stress and inflammation.[89] Additionally, inverse associations between the metabolite networks of coffee intake and obesity were noted, eluding to possible metabolic pathways that explain the potential protective effects of coffee on obesity development.[89, 90] Metabolites of branched chain amino acids (BCAA) have also gained popularity in metabolomics research, with increasing evidence demonstrating their functional role in promoting metabolic changes that contribute to risk of CVD,[91] metabolic syndrome,[92] pre-diabetes,[93] type-2 diabetes,[91, 93, 94] and stroke.[95] In this regard, a host of other metabolites have been found to be predictive various metabolic risk phenotypes in response to diet change, including inter-individual variation in blood pressure,[88] incident hypertension,[96] and various types of cancers[97, 98].

Recent endeavors in the personalized nutrition agenda have concentrated focus on optimizing the intestinal microflora environment through diet. Since being recognized as an independent risk factor of obesity,[85, 99] the gut microbiota has been extensively studied with consistent evidence suggesting distinctions in microbial environments across different dietary habits and patterns backgrounds may unveil critical insights regarding the dietary, genetic and metabolic potential of the intestinal tract in modulating disease risk and progression.[100] Lower microbial composition and diversity, in particular, has been observed among diets enriched in animal-fat and diet patterns characteristic of a westernized diet (e.g., high- fat whole milk, sugar-sweetened drinks, higher total energy and carbohydrate intake), whereas greater microbial diversity has been observed among individuals habitually consuming greater quantities of fibers consumed through fruit, legumes, and vegetables.[101-103] Importantly the microbial benefit elicited from greater plant-based food consumption has been observed even in the backdrop of a conventional, "less-healthy" Westernized dietary pattern, suggesting beneficial regulation of microbial metabolism by the gut in response to habitually practiced- healthier diet behaviors.[104] Along these lines, specific intestinal metabolites produced via metabolism of red meat have also been correlated to atherosclerosis and CVD pathogenesis,[94, 105] providing mechanistic support to previous findings that have linked vegetarian and vegan[106] or Mediterranean diets- which emphasize low red meat consumption[107], with reduced CVD risk[27].

As the volume of research investigating the gut microbial ecology continues to increase, so does our understanding of the complex interplay that exists between diet pattern and behavior-, genes- and the gut microbiome- in modulating individual chronic disease risk. Notwithstanding, preliminary evidence has shown that both composition and diversity of the gut microbiota responds to *short-term* changes in diet, speaking to the importance that the gut microbiome is

able to respond rapidly to sudden alterations made in the diet in response to intervention or changes in lifestyle.[102, 108] Thus, while gut microbiome profiling is still in its infancy, substantial progress has been made in understanding the pivotal role of the gut microbiota in overall health and disease, and the influence that specific dietary components have in strengthening or perturbing the microbial community.[100] As such, dietary modulation on the gut microbiome has the potential to change an individual's health trajectory and ultimately risk of disease, which may prove to be even stronger than one's genetic makeup alone. Continued advances in gut microbiome research will be fundamental to testing existing nutritional therapeutics, such as pro- and pre-biotics, for the treatment of metabolic conditions.[81] Likewise, integrating gut microbiome profiling with other disciplines of precision nutrition, such as nutritgenetics and metabolomics, provides tremendous potential to identify other nutritional and metabolic targets that will aid in the refinement of disease risk stratification and prevention.

Precision for weight loss

Weight loss though lifestyle modification is the primary strategy prescribed to treat obesity and its related co-morbidities. Not surprisingly, individual efforts to lose weight are challenged by the temptations rendered in today's obesogenic environment. To this regard, adaptations to more contemporary lifestyles further propagate unhealthy lifestyle behavior practice (e.g., increased sedentariness, poor eating behaviors, sleep deprivation) making excess weight gain inevitable, and further increasing risk of developing metabolic disease. Despite decades worth of obesity-prevention research, there has been limited success showing that, after study completion intentional weight loss continues or is maintained, or any weight re-gained is minimal. To this regard, challenges in demonstrating long-term effectiveness from dietary interventions has supported the view that individual proneness, and hence genotypes, to obesity,

weight loss and weight regain, along with environment, may elicit greater consequence in shaping weight change success and overall metabolic disease risk.[109-111] With the inception of new precision medicine initiatives, and recent progress in genome-wide association studies (GWAS), emerging research has focused on uncapping the genetic determinants of body weight,[109] primarily with respect to genes that regulate energy expenditure regulation, appetite control, lipid metabolism and adipogenesis.[111, 112] Keeping with the theme of "tailored" modification, precision weight-loss approaches have since been developed, underscoring the notion that weight loss prognosis may be more effective for some genotypes than others,[113] and that both, genetic makeup and genetic responses to diet (*or other lifestyle modifications*) at least partially explain an individual's obesity fate, and hence susceptibility to metabolic disorders. Given that obesity poses on the greatest risks to metabolic diseases (e.g., metabolic syndrome, type-2 diabetes, CVD, etc.), it is no surprise that the interplay between diet and candidate genes predictive of obesity risk (e.g., FTO; MC4R; PPARɣ; MTHFR PLIN1)[85, 114-116], are capable of changing the overall trajectory of specific metabolic traits. To date, several investigations from both observational and randomized control trials, including those from landmark trials, LOOK AHEAD,[117] POUNDS LOST[109, 118-120], and the Diabetes Prevention Program[121], among others[122, 123], have confirmed that significant interactions exist between diet and obesity-associated risk genes, and these interactions, in turn, play a critical role in modulating individual's weight loss response to different dietary interventions.[109, 111] For example, evidence from two large cohort studies[122, 124] indicate carriers of a risk allele on various candidate obesity genes who followed an energy-restrictive high protein diet experienced significantly greater reductions in weight loss, less weight regain[122], and significant reductions in visceral adipose tissue mass as well as superficial adipose tissue compared to non-carriers and those following a low-protein diet at 6-

month. These data suggest a particular genetic effect on overall body fat and fat distribution that may be used to identify individuals who may benefit the most from high protein diet interventions. In the POUNDS-LOST trial, significant interactions found between carbohydrate intake and a weight-loss allele located on an insulin receptor gene indicate one possible mechanistic explanation as to why carriers of the weight-loss risk genetic variant assigned to a high-carbohydrate, low-fat diet benefited more in terms of greater weight loss and improvements in insulin resistance than those without this genotype.[119] Several other metabolic phenotypes, including hypertension,[125] and metabolic syndrome [120] have similarly been shown to be influenced by the interaction between dietary intervention and metabolic gene variants.[109] In this context, the same obesity-related genetic variants that have been linked to weight loss are believed to be predictive of weight rebound[113], as evidenced by studies that evaluated weight-regain following 6 month,[122] one-[117] and two-year[126, 127] evaluations post intervention. Taken together, these findings confirm the existence of a genetic determinant in response to dietary modification for intentional weight loss and body-weight stability as well as prevention of obesity. However, the limited replicability across study findings[109, 113, 121, 123] suggests results are still too premature to include genetic screening in the design of individualized weight-loss prescriptions.[113] Nonetheless, novel insights have been gained regarding the etiology of obesity in response to the individual dietary "environment", and the implications of specific diet-gene interactions in predicting weight loss prognosis. Although still in the preliminary stages, evidence to date has provided a compelling argument for precision-weight loss prescriptions for optimizing individual weight loss efficacy, and protection from disease or disease progression.

Precision for not smoking

Tobacco use is the leading cause of preventable death worldwide[128], with more than 480,000 tobacco-related deaths per year in the United States alone.[129] Smoking increases

morbidity and mortality from a range of chronic diseases including cancer, heart disease, stroke, and chronic obstructive pulmonary disease.[129] Given these adverse health risks, a common sentiment among healthcare providers is that "it's just common sense" to quit smoking.[130] Contrary to this notion, smoking is far from a simple behavioral choice. Smokers are generally aware of the potential health complications and want to quit[129, 131], but only 3-5% of quit attempts lead to prolonged abstinence.[132] Although advising patients to quit smoking is considered a critical element of tobacco reduction programs[133, 134], relying solely on advice-giving is likely to be inadequate to promote health behavior change in the majority of cases.[135] This is because the initiation and persistence of smoking are determined by a complex interplay among biological, psychological, and sociocultural factors, including the highly addictive properties of nicotine.[128, 136]

A precision medicine approach can be used to develop and implement smoking cessation interventions to match unique characteristics of an individual. For example, the Transtheoretical Model (TTM)[137] has gained popularity since the 1980s as a conceptual framework to match intervention strategies to a patient's level of readiness to quit smoking. The TTM assumes that individuals progress through a sequence of discrete motivational stages in their movement toward behavior change, and assumes that interventions should emphasize specific processes at each stage.[137] In other words, patient-provider conversations about tobacco cessation should "look different" depending on whether a patient is not ready to quit, is preparing to quit, has achieved continuous abstinence, or is dealing with a relapse. Empirical evidence for the TTM has been mixed, with a 2010 Cochrane Review of 41 trials concluding that TTM-based interventions for smoking cessation, on average, "were neither more nor less effective than their non-stage-based equivalents".[138] Some have also argued that the TTM may inadvertently prompt clinicians

to completely avoid intervening with "precontemplators" who are apparently not ready to consider quitting.[139] Despite the need for more high-quality research to clarify inconsistent findings, the TTM model draws attention to the importance of understanding patients' perceptions about tobacco use in an effort to optimize intervention effectiveness.

Attitudes and self-efficacy are two other constructs from mainstream health behavior theories that are frequently used to tailor smoking cessation interventions.[140] The degree to which individuals have favorable evaluations of tobacco use and feel confident in their ability to quit can influence behavioral intentions and the likelihood of successful cessation.[141-143] Individuals report smoking for a variety of reasons including emotion regulation, social approval, weight management, avoidance of withdrawal symptoms, and/or boredom.[144] Understanding individuals' reasons for smoking is important, given that these reasons often serve as barriers to initial quit attempts and long-term abstinence.[145] Several brief interventions, such as motivational interviewing[146, 147] and the 5R model[134], provide guidance on how to enhance self-efficacy and bolster positive attitudes toward quitting among people who are ambivalent about treatment.

Additional examples have been described regarding how to address individualized barriers to smoking cessation. Concern about cessation-induced weight gain, for example, is related to lower intention to quit and poorer cessation outcomes.[148, 149] Cognitive-behavioral therapy to reduce weight concerns has been demonstrated to improve continuous abstinence when delivered to women concerned about weight gain from a quit attempt.[150] Helping patients develop emotion regulation skills can also support quit attempts in some individuals, as demonstrated by research showing that integrating standard treatment (e.g., nicotine replacement therapy) with psychological treatments for patients with psychiatric comorbidity can enhance the

likelihood of smoking cessation.[151-153] In addition to addressing individualized concerns about weight or mental health, matching the goals (e.g., to quit vs. to cut down) and modality (e.g., pharmacotherapy, professional support, "cold turkey") of treatment to patient preferences may enhance motivation to quit.[153-155]

Cultural factors also influence perceptions about the benefits and risks of smoking, and predict individuals' susceptibility to tobacco dependence.[136] There have been efforts to tailor messaging within multifaceted tobacco interventions to Indigenous[156], Hispanic[157], and African American[158, 159] populations by integrating culturally relevant values, views, spiritual elements, and language. Culture-related differences in tobacco use are influenced not just by cultural norms about the acceptability of tobacco, but also relate to differences in nicotine metabolism, socioeconomic status, and access to tobacco control interventions.[136] For example, Black smokers demonstrate higher levels of serum cotinine than their White or Mexican-American counterparts, suggesting one potential mechanism accounting for their lower success with quitting smoking.[160] With increasing multiculturalism across the world, there is a need for continued research to determine the effectiveness and feasibility of culturally targeted tobacco reduction programs.

A variety of effective medications for tobacco reduction are available to double or triple the likelihood of abstinence[155], and combining behavioral treatment with pharmacotherapy can produce 25-30% abstinence rates.[134] Despite advances in smoking cessation treatments, a significant subset of patients do not achieve long-term abstinence, suggesting a need to continue investigating novel methods to identify and treat tobacco use. Biomarkers, such as the α5-α3-α4 nicotinic receptor subunit gene cluster, have been identified as important contributors to nicotine dependence that could guide personalized medicine for smoking cessation.[161] Further, mobile

technologies have been used to tailor smoking cessation messaging to individuals' unique patterns of lapse risk factors as they engage in their everyday activities.[162-164] There is no "one-size-fits-all" approach to smoking cessation treatment; individual differences in motivation, nicotine dependence, preferences, biological predilection, and sociocultural characteristics must be considered to optimally address the health burden of tobacco use.

Key Supportive Components for Precision in Healthy Living Medicine

The Built Environment

Simply defined, the built environment includes the major physical spaces, including buildings, streets, homes and infrastructure in which we live, work, receive an eduation and play.[165] Profound changes to the built environment, particularly over recent generations, have had a significant impact on lifestyle practices of many individuals and populations. In turn, these practices have had serious downstream health consequences. Over time, the major reconfiguration of lifestyle behaviors, including as a function of changes to our built environment, have resulted in dramatic decreases in PA levels across the lifespan, often clustered with other poor behaviors including unhealthy eating practices. Taken together, these primary changes to lifestyle behaviors have been the main drivers of a positive energy balance, predisposition to increased overweight and obesity and CVD.[166-168] An estimated 1 in 3 adults globally do not meet the minimum weekly PA levels recommended for protective health benefits.[169] This equates to a staggering 1.5 billion adults with the potential to improve their health status and reduce the risks associated with chronic diseases, simply as a function of increasing their PA level.[170]

From an historical perspective, changes to the built environment have coincided with reductions in population PA, including the most common form of activity for people of all ages,

walking. Fundamental changes in technology in the built environment, including increased mechanization, urbanization, transportation, and globalization have been major contributors to the dramatic declines in walking in both the developed and developing world. A primary example is the increased availability of motor cars and other motorized vehicles responsible for displacing active transport for people of all ages. In addition, particularly in urban settings, safety and walkability has been seriously compromised due to increased congestion and attendant pollution, typically associated with an increased reliance on motor vehicles.

In a recent Lancet Series on urban design, transport and health, Giles-Corti et al.[171] identified a set of eight interventions with the greatest likelihood of encouraging active transport (walking, cycling and use of public transport). Importantly, if combined these interventions including pedestrian- and cycling-friendly networks, and desirability of active transport, would assist in healthier and more sustainable urban settings. Evidence suggests that some of the most important causes of numerous global health problems include poor policy and design features of the built environment.[172] For example, chronic disease and injury prevalence is influenced by land use and transport policies through increases in pollution, noise, social isolation and low levels of PA/sedentary behaviors.[173]

If we agree that the built environment discourages PA and encourages unhealthy eating, urgent attention is required to address the policies and practices that affect the built environment in order to underpin healthy living principles.[165]

Communicative Contexts in Health

Communicative contexts are factors of influence on HL outcomes from a communication perspective. The factors accounted for are the mass media environment, the interpersonal

networks of discussion, the social media environment, the technology environment, and the physical environment.

The mass media includes news, social advertising efforts, as well as commercial advertising. For instance, exposure to health news can influence awareness and health literacy, but also attitudes through persuasive elements in the news like framing.[174] Several studies have shown that frames about the causes of obesity (personal vs. societal) have consequences for whom individuals perceive to be responsible for the problem, which can influence support for public policies.[175, 176] Mass media campaigns have great potential across large populations in curbing undesirable behaviors like consumption of tobacco or high-calorie foodstuffs and producing desirable behaviors such as increasing PA or eating more fruits and vegetables.[177] The back drop of commercial advertising is still omnipresent and its effects are remarkable; for each public service and on TV, there are 400 ads from industry whose share of unhealthy foods is 95%.[178]

Another key communicative context is our interpersonal networks of discussion, also referred to as everyday talk. Everyday talk is both formal and informal, has direct consequences on HL practices and the dissemination of information and values, serves to negotiate meaning and labels about health concerns and defines relationships with healthcare providers.[179] Those effects can be both desirable (e.g., we learn that we are not exercising enough) and undesirable (e.g., we engage in risky behavior such as smoking).

Recently, interpersonal networks have expanded and merged with mass media with the arrival and diffusion of social networking sites. Social media networks may overlap with interpersonal ones, but they also offer the possibility to interact with strangers as well as distant and local friends or family. Because of its reach and tools to manage privacy and self-

presentation, social media can be considered as separate from interpersonal networks of communication. Overall, social media use is heavy among young adults (≈88%) and progressively decreases in older generations[180], but what is more important is the prevalence of social media in everyday life - ~50% of social media users check these sites several times a day. The effects of social media on health and wellbeing depend on the medium and whether they reflect ongoing campaigns[181, 182] or are organically created within the social network.[183]

In addition to affecting HLM outcomes, communicative contexts influence each other—thereby *also* mediating some of the effects on HL. For instance, the literature on food environments has shown that having difficulty accessing healthy foods in one's community negatively affects the consumption of those foods. However, the food environment also has adverse effects on interpersonal discussions of food and nutrition as well as exposure to and reflection of news about the effects of what people eat and drink.[184] These effects, in turn, negatively fuel the decrease in healthy foods consumption, thus creating a vicious cycle. To improve efficacy, HLM requires a multi-pronged approach in which all these contexts are considered and measured together.

Leveraging Technologic Advances

The use of web-based and mobile health (mHealth; interactive voice response calls, short message service, or text messaging, and smartphone applications) platforms continue to expand, providing great opportunities to further refine the delivery of HLM. Current evidence suggests the use of technology has the potential to improve healthy lifestyle patterns such as increasing PA and consuming a healthier diet.[5, 185-188] For example, using a web-, tablet- or smartphone-based HLM intervention, in conjunction with health coaching, has also been shown to result in significant weight loss in a Medicare cohort at risk for diabetes.[189] As defined by the World

Health Organization, mHealth is "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices".[190] Developed in iterations, mHealth platforms target audience-specific behaviors and can change responsively with the needs of both the users and the creators. Where general technology provides open access to information, mHealth can specify content and provide a supportive management system that suggests personalized care and newer, more relevant guidance while reaching a large and continually growing proportion of the global population. In prior studies evaluating mHealth tools within HLM, applications commonly deliver background education, personalized goal-setting, and multiple avenues of user motivation.[191-193] However, while these three pieces are vital to each platform and show great potential for HLM results, mHealth tools require well-designed user interfaces and purposes based on satisfactory, comprehendible data to have valid results.[192] Considering low participant cost in addition to the rapid pace of mHealth development, well-designed platforms can transition patients into behavioral changes by including even small opportunities for personalization.

There is also great potential for web-based and mHealth platforms that deliver HLM to incorporate an artificial intelligence (AI) backbone, further enhancing the precision and effectiveness of HL interventions. Targeting multiple behaviors within HLM, AI applications go beyond what traditional educational resources or interventions can do by both giving to and responding to users. This form of reflexive technology design can imply compassion and acknowledgment of a user's lifestyle decisions, affording health professional-controlled patient accountability without the risk of communication influences or excuses on physical difficulty.[194, 195] Research into the effectiveness of AI to improve HL characteristics has begun and is showing

promising results.[193-196] In the spirit of precision medicine, the use of technology in HLM will not be a one-size-fits-all approach. Individual preferences and available resources must be considered when determining the optimal use of technology in a personalized care plan for HL.

Health care professionals delivering HLM must leverage technology to enhance the number of touchpoints they have with individuals under their care. Technologic advances will occur rapidly and, as such, health care professionals must remain current and titrate their use of technology as more effective platforms emerge. With the emergence and falling prices of wearable technology, publicly available sensory devices can collect real-time health data specific to individual HLM goals. Not only will these devices provide access to many physiological parameters of an individual receiving care, they can also influence the content personalization of smartphone apps and behaviors of responsive AI.[197] Opportunities provided by mHealth development can directly respond to communicative and physical influences surrounding HLM and corresponding outcomes.

How does healthy living influence precision medicine genomics?

To this point, the primary focus of precision medicine has been on identifying genetic alterations that are associated with various diseases. However, genomic studies have limitations in that they only measure a fraction of the genome, and genes and their products typically do not act alone, but with other genes and proteins in a specific environment.[198] The combination of individual genetic variants with environmental factors creates a highly individualized disease phenotype. Additionally, environmental factors, such as the components of HL, can modify disease risk even when genetic variations are present.[29, 199-201] Understanding the interplay of social and environmental factors with an individual's biology, will allow for the development of highly individualized disease phenotypes and ultimately more accurate diagnoses, more rational

disease prevention strategies, better treatment selection, and the development of novel therapies.[202]

Several studies have examined the relationship between HL and lowering chronic disease risk in individuals who are genetically prone to developing disease. The Diabetes Prevention Program (DPP) study[201] and The Finnish Diabetes Prevention Study[200] both recruited individuals with a high risk to develop diabetes and both found that a lifestyle program consisting of diet and exercise counseling reduced diabetes risk by 58%. Additionally, the HL program in the DPP study reduced risk significantly more than treatment with metformin (31%).[201] The American Cancer Society (ACS) recommends at least 150 min of moderate-intensity PA per week, alcohol intake of ≤1 drink per day, and maintaining a BMI of ≤25 kg/m^2 for breast cancer prevention.[199] Cloud et al. examined the mortality risk of women from the high-risk Breast Cancer Family Registry in New York who adhered to the ACS recommendations.[199] Adherence to all three ACS recommendations was associated with 44–53 % lower mortality in women unaffected with breast cancer at baseline and in women affected with breast cancer at baseline.[199] Lastly, Khera et al. examined the extent to which increased genetic risk of coronary artery disease (CAD) can be offset by a HL.[29] Three prospective cohorts had their genetic risk for CAD determined and were placed in either a high, intermediate, or low risk category. A favorable lifestyle was defined as meeting at least three of the four HL factors: 1) no smoking; 2) no obesity; 3) PA at least once weekly; and 4) a healthy diet pattern. Regardless of risk group, a favorable lifestyle was associated with a lower risk of coronary events including a 46% reduction in the high genetic risk group.[29]

Collectively, these four studies highlight how lifestyle and environmental factors, impacts precision medicine genomics. To achieve the goals of the precision medicine initiative, we must

gain a more detailed understanding how genetic risk and treatment responses modify the disease phenotype. Applying 'omics' approaches and in-depth phenotyping after HLM interventions will allow for the classification of patients with respect to disease susceptibility, subclass of disease or the likelihood of a positive or adverse response to a specific therapy and further the precision medicine initiative.

Conclusions

In conclusion, leading a healthy lifestyle is of central importance to both preventing and treating a host of chronic diseases, including CVD. Assisting individual to adopt HL practices is not a one-size-fits-all approach. Any movement toward a healthier behavior portends significant health benefits. As such, employing a precision approach in the prescription of the HL polypill, the key ingredients of which are moving more, consuming a nutritious diet, maintaining a healthy body weight and not smoking, will enhance adoption and long-term adherence.

References

1. Arena R and Lavie CJ. Preventing Bad and Expensive Things From Happening by Taking the Healthy Living Polypill: Everyone Needs This Medicine. *Mayo Clin Proc*. 2017;92:483-487.

2. Arena R, McNeil A, Sagner M and Lavie CJ. Healthy Living: The Universal and Timeless Medicine for Healthspan. *Prog Cardiovasc Dis*. 2017;59:419-421.

3. Kones R and Rumana U. Cardiometabolic diseases of civilization: history and maturation of an evolving global threat. An update and call to action. *Annals of medicine*. 2017:1-15.

4. Gonzalez-Chica DA, Grande ED, Bowden J, Musker M, Hay P and Stocks N. Are we reducing the risk of cardiovascular disease and improving the quality of life through preventive health care? Results of a population-based study in South Australia. *Prev Med*. 2017.

5. Sagner M, McNeil A, Puska P, Auffray C, Price ND, Hood L, Lavie CJ, Han ZG, Chen Z, Brahmachari SK, McEwen BS, Soares MB, Balling R, Epel E and Arena R. The P4 Health Spectrum - A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan. *Prog Cardiovasc Dis*. 2017;59:506-521.

6. Akesson A, Larsson SC, Discacciati A and Wolk A. Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men: a population-based prospective cohort study. *J Am Coll Cardiol*. 2014;64:1299-306.

7. Larsson SC, Akesson A and Wolk A. Primary prevention of stroke by a healthy lifestyle in a high-risk group. *Neurology*. 2015;84:2224-8.

8. Younus A, Aneni EC, Spatz ES, Osondu CU, Roberson L, Ogunmoroti O, Malik R, Ali SS, Aziz M, Feldman T, Virani SS, Maziak W, Agatston AS, Veledar E and Nasir K. A Systematic Review of the Prevalence and Outcomes of Ideal Cardiovascular Health in US and Non-US Populations. *Mayo Clin Proc*. 2016;91:649-70.

9. Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, Kaptoge S, Di Angelantonio E, Stampfer M, Willett WC and Hu FB. Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. *Circulation*. 2018.

10. Alter DA, Bing Y, Bajaj RR and Oh PI. The Relationship Between Cardiac Rehabilitation Participation and Health Service Expenditures within a Universal Health Care System. *Mayo Clin Proc*. 2017.

11. Anderson L and Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. *The Cochrane database of systematic reviews*. 2014;12:CD011273.

12. Armstrong MJ, Sigal RJ, Arena R, Hauer TL, Austford LD, Aggarwal S, Stone JA and Martin BJ. Cardiac rehabilitation completion is associated with reduced mortality in patients with diabetes and coronary artery disease. *Diabetologia*. 2015;58:691-8.

13. Balady GJ, Ades PA, Bittner VA, Franklin BA, Gordon NF, Thomas RJ, Tomaselli GF, Yancy CW, American Heart Association Science A and Coordinating C. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association. *Circulation*. 2011;124:2951-60.

14. Arena R, Lavie CJ and Guazzi M. Prescribing a Healthy Lifestyle Polypill With High Therapeutic Efficacy in Many Shapes and Sizes. *American Journal of Lifestyle Medicine*. 2017;11:476-478.

15. Arena R, Whitsel LP, Berra K, Lavie CJ, Kaminsky L, Williams M, Hivert MF, Franklin NC, Myers J, Dongel D, Lloyd-Jones DM, Guazzi M, Pinto FJ, Consentino F, Halle M, Gielen S, Dendale P, Niebauer J, Pelliccia A, Giannuzzi P, Corra U, Piepoli M, Lianov L, Guthrie G and Shurney D. Healthy Lifestyle Interventions to Combat Non-Communicable Disease: A Novel Non-Hierarchical Connectivity Model for Key Stakeholders: A Policy Statement from the AHA, ESC, EACPR and ACPM. *Mayo Clin Proc*. 2015;90:1082-1103.

16. Lee DC, Brellenthin AG, Thompson PD, Sui X, Lee IM and Lavie CJ. Running as a Key Lifestyle Medicine for Longevity. *Prog Cardiovasc Dis*. 2017.

17. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, Casanova A, Swaminathan S, Anjana RM, Kumar R, Rosengren A, Wei L, Yang W, Chuangshi W, Huaxing L, Nair S, Diaz R, Swidon H, Gupta R, Mohammadifard N, Lopez-Jaramillo P, Oguz A, Zatonska K, Seron P, Avezum A, Poirier P, Teo K and Yusuf S. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet*. 2017.

18. Troesch B, Biesalski HK, Bos R, Buskens E, Calder PC, Saris WH, Spieldenner J, Verkade HJ, Weber P and Eggersdorfer M. Increased Intake of Foods with High Nutrient Density Can Help to Break the Intergenerational Cycle of Malnutrition and Obesity. *Nutrients*. 2015;7:6016-6037.

19. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG and Remington PL. Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. *Ann Intern Med*. 2015.

20. Kraus WE, Bittner V, Appel L, Blair SN, Church TS, Despres JP, Franklin BA, Miller TD, Pate RR, Taylor-Piliae RE, Vafiadis DK and Whitsel LP. The National Physical Activity Plan: A Call to Action From the American Heart Association: A Science Advisory From the American Heart Association. *Circulation*. 2015;131.

21. Arena R, Lavie CJ, Hivert MF, Williams MA, Briggs PD and Guazzi M. Who will deliver comprehensive healthy lifestyle interventions to combat non-communicable disease? Introducing the healthy lifestyle practitioner discipline. *Expert review of cardiovascular therapy*. 2016;14:15-22.

22. Arena R, McNeil A, Street S, Bond S, Laddu DR, Lavie CJ and Hills AP. Let Us Talk About Moving: Reframing the Exercise and Physical Activity Discussion. *Current problems in cardiology*.

23. Van Horn L, Carson JAS, Appel LJ, Burke LE, Economos C, Karmally W, Lancaster K, Lichtenstein AH, Johnson RK, Thomas RJ, Vos M, Wylie-Rosett J and Kris-Etherton P. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e505-e529.

24. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD, American Heart Association Strategic Planning Task F and Statistics C. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586-613.

25. Warburton DE and Bredin SS. Reflections on Physical Activity and Health: What Should We Recommend? *Can J Cardiol*. 2016;32:495-504.

26. Miller V, Mente A, Dehghan M, Rangarajan S, Zhang X, Swaminathan S, Dagenais G, Gupta R, Mohan V, Lear S, Bangdiwala SI, Schutte AE, Wentzel-Viljoen E, Avezum A, Altuntas Y, Yusoff K, Ismail N, Peer N, Chifamba J, Diaz R, Rahman O, Mohammadifard N, Lana F, Zatonska K, Wielgosz A, Yusufali A, Iqbal R, Lopez-Jaramillo P, Khatib R, Rosengren A, Kutty VR, Li W, Liu J, Liu X, Yin L, Teo K, Anand S, Yusuf S, Diaz R, Orlandini A, Linetsky B, Toscanelli S, Casaccia G, Cuneo JMM, Rahman O, Yusuf R, Azad AK, Rabbani

KA, Cherry HM, Mannan A, Hassan I, Talukdar AT, Tooheen RB, Khan MU, Sintaha M, Choudhury T, Haque R, Parvin S, Avezum A, Oliveira GB, Marcilio CS, Mattos AC, Teo K, Yusuf S, Dejesus J, Agapay D, Tongana T, Solano R, Kay I, Trottier S, Rimac J, Elsheikh W, Heldman L, Ramezani E, Dagenais G, Poirier P, Turbide G, Auger D, De Bluts AL, Proulx MC, Cayer M, Bonneville N, Lear S, Gasevic D, Corber E, de Jong V, Vukmirovich I, Wielgosz A, Fodor G, Pipe A, Shane A, Lanas F, Seron P, Martinez S, Valdebenito A, Oliveros M, Wei L, Lisheng L, Chunming C, Xingyu W, Wenhua Z, Hongye Z, Xuan J, Bo H, Yi S, Jian B, Xiuwen Z, Xiaohong C, Tao C, Hui C, Xiaohong C, Qing D, Xiaoru C, Qing D, Xinye H, Bo H, Xuan J, Jian L, Juan L, Xu L, Bing R, Yi S, Wei W, Yang W, Jun Y, Yi Z, Hongye Z, Xiuwen Z, Manlu Z, Fanghong L, Jianfang W, Yindong L, Yan H, Liangqing Z, Baoxia G, Xiaoyang L, Shiying Z, Rongwen B, Xiuzhen T, Dong L, Di C, Jianguo W, Yize X, Tianlu L, Peng Z, Changlin D, Ning L, Xiaolan M, Yuqing Y, Rensheng L, Minfan F, Jing H, Yu L, Xiaojie X, Qiang Z, Lopez-Jaramillo P, Lopez PAC, Garcia R, Jurado LJA, Gómez-Arbeláez D, Arguello JF, Dueñas R, Silva S, Pradilla LP, Ramirez F, Molina DI, Cure-Cure C, Perez M, Hernandez E, Arcos E, Fernandez S, Narvaez C, Paez J, Sotomayor A, Garcia H, Sanchez G, David T, Rico A, Mony P, Vaz M, Bharathi AV, Swaminathan S, Kurpad KSAV, Jayachitra KG, Kumar N, Hospital HAL, Mohan V, Deepa M, Parthiban K, Anitha M, Hemavathy S, Rahulashankiruthiyayan T, Anitha D, Sridevi K, Gupta R, Panwar RB, Mohan I, Rastogi P, Rastogi S, Bhargava R, Kumar R, Thakur JS, Patro B, Lakshmi PVM, Mahajan R, Chaudary P, Kutty VR, Vijayakumar K, Ajayan K, Rajasree G, Renjini AR, Deepu A, Sandhya B, Asha S, Soumya HS, Kelishadi R, Bahonar A, Mohammadifard N, Heidari H, Yusoff K, Ismail TST, Ng KK, Devi A, Nasir NM, Yasin MM, Miskan M, Rahman EA, Arsad MKM, Ariffin F, Razak SA, Majid FA, Bakar NA, Yacob MY, Zainon N, Salleh R, Ramli MKA, Halim NA, Norlizan SR, Ghazali NM, Arshad MN, Razali R, Ali S, Othman HR, Hafar C, Pit A, Danuri N, Basir F, Zahari SNA, Abdullah H, Arippin MA, Zakaria NA, Noorhassim I, Hasni MJ, Azmi MT, Zaleha MI, Hazdi KY, Rizam AR, Sazman W, Azman A, Khatib R, Khammash U, Khatib A, Giacaman R, Iqbal R, Afridi A, Khawaja R, Raza A, Kazmi K, Zatonski W, Szuba A, Zatonska K, Ilow R, Ferus M, Regulska-Ilow B, Rózanska D, Wolyniec M, Alkamel, Ali M, Kruger MA, Voster HH, Schutte AE, Wentzel-Viljoen E, Eloff FC, de Ridder H, Moss H, Potgieter J, Roux AA, Watson M, de Wet G, Olckers A, Jerling JC, Pieters M, Hoekstra T, Puoane T, Igumbor E, Tsolekile L, Sanders D, Naidoo P, Steyn N, Peer N, Mayosi B, Rayner B, Lambert V, Levitt N, Kolbe-Alexander T, Ntyintyane L, Hughes G, Swart R, Fourie J, Muzigaba M, Xapa S, Gobile N, Ndayi K, Jwili B, Ndibaza K, Egbujie B, Rosengren A, Boström KB, Gustavsson A, Andreasson M, Snällman M, Wirdemann L, Oguz A, Imeryuz N, Altuntas Y, Gulec S, Temizhan A, Karsidag K, Calik KBT, Akalin AAK, Caklili OT, Keskinler MV, Erbakan AN, Yusufali AM, Almahmeed W, Swidan H, Darwish EA, Hashemi ARA, Al-Khaja N, Muscat-Baron JM, Ahmed SH, Mamdouh TM, Darwish WM, Abdelmotagali MHS, Awed SAO, Movahedi GA, Hussain F, Al Shaibani H, Gharabou RIM, Youssef DF, Nawati AZS, Salah ZARA, Abdalla RFE, Al Shuwaihi SM, Al Omairi MA, Cadigal OD, Alejandrino RS, Chifamba J, Gwaunza L, Terera G, Mahachi C, Murambiwa P, Machiweni T and Mapanga R. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *The Lancet*. 390:2037-2049.

27. Committee NRC. National Research Council *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* Washington (DC): National Academies Press (US). 2011.

28. Mutie PM, Giordano GN and Franks PW. Lifestyle precision medicine: the next generation in type 2 diabetes prevention? *BMC medicine*. 2017;15:171.

29. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, Fuster V, Boerwinkle E, Melander O, Orho-Melander M, Ridker PM and Kathiresan S. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *N Engl J Med*. 2016;375:2349-2358.

30. Sin NL, Kumar AD, Gehi AK and Whooley MA. Direction of Association Between Depressive Symptoms and Lifestyle Behaviors in Patients with Coronary Heart Disease: the Heart and Soul Study. *Annals of Behavioral Medicine*. 2016;50:523-32.

31. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S and investigators I. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:953-62.

32. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *American Journal of Preventive Medicine*. 2002;23:51-61.

33. Gump BB, Matthews KA, Eberly LE, Chang YF and Group MR. Depressive symptoms and mortality in men: results from the Multiple Risk Factor Intervention Trial. *Stroke*. 2005;36:98-102.

34. Nicholson A, Kuper H and Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27:2763-74.

35. Barefoot JC and Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*. 1996;93:1976-80.

36. Lesperance F, Frasure-Smith N, Juneau M and Theroux P. Depression and 1-year prognosis in unstable angina. *Archives of Internal Medicine*. 2000;160:1354-60.

37. Lesperance F, Frasure-Smith N, Talajic M and Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*. 2002;105:1049-53.

38. Mavrides N and Nemeroff C. Treatment of depression in cardiovascular disease. *Depression & Anxiety*. 2013;30:328-41.

39. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, Schatzberg AF, Sudheimer K, Keller J, Mayberg HS, Gunning FM, Alexopoulos GS, Fox MD, Pascual-Leone A, Voss HU, Casey BJ, Dubin MJ and Liston C. Erratum: Resting-state connectivity biomarkers define neurophysiological subtypes of depression.[Erratum for Nat Med. 2017 Jan;23 (1):28-38; PMID: 27918562]. *Nature Medicine*. 2017;23:264.

40. Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, Kinkead B, Nemeroff CB and Mayberg HS. Functional Connectivity of the Subcallosal Cingulate Cortex And Differential Outcomes to Treatment With Cognitive-Behavioral Therapy or Antidepressant Medication for Major Depressive Disorder.[Erratum appears in Am J Psychiatry. 2017 Jun 1;174(6):604; PMID: 28565951]. *American Journal of Psychiatry*. 2017;174:533-545.

41. Christensen P. *Patient Adherence to Medical Treatment Regimens: Bridging the Gap Between Behavioral Science and Biomedicine*. New Haven, CT: Yale University Press; 2004.

42. Riegel B, Moser DK, Buck HG, Dickson VV, Dunbar SB, Lee CS, Lennie TA, Lindenfeld J, Mitchell JE, Treat-Jacobson DJ, Webber DE, American Heart Association Council on C, Stroke N, Council on Peripheral Vascular D, Council on Quality of C and Outcomes R. Self-Care for the Prevention and Management of Cardiovascular Disease and Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Journal of the American Heart Association*. 2017;6:31.

43. Lawlor DA and Hanratty B. The effect of physical activity advice given in routine primary care consultations: a systematic review. *Journal of Public Health Medicine*. 2001;23:219-26.

44. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM and Diabetes Prevention Program Research G. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New Engl J Med*. 2002;346:393-403.

45. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, Miller CD, Ziemer DC and Barnes CS. Clinical inertia. *Annals of Internal Medicine*. 2001;135:825-34.

46. Lavoie KL, Rash JA and Campbell TS. Changing Provider Behavior in the Context of Chronic Disease Management: Focus on Clinical Inertia. *Annual Review of Pharmacology & Toxicology*. 2017;57:263-283.

47. Rubak S, Sandbaek A, Lauritzen T and Christensen B. Motivational interviewing: a systematic review and meta-analysis. *British Journal of General Practice*. 2005;55:305-12.

48. McGrane N, Galvin R, Cusack T and Stokes E. Addition of motivational interventions to exercise and traditional physiotherapy: a review and meta-analysis. *Physiotherapy*. 2015;101:1-12.

49. Armstrong MJ, Mottershead TA, Ronksley PE, Sigal RJ, Campbell TS and Hemmelgarn BR. Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. *Obesity Reviews*. 2011;12:709-23.

50. Artinian NT, Fletcher GF, Mozaffarian D, Kris-Etherton P, Van Horn L, Lichtenstein AH, Kumanyika S, Kraus WE, Fleg JL, Redeker NS, Meininger JC, Banks J, Stuart-Shor EM, Fletcher BJ, Miller TD, Hughes S, Braun LT, Kopin LA, Berra K, Hayman LL, Ewing LJ, Ades PA, Durstine JL, Houston-Miller N, Burke LE and American Heart Association Prevention Committee of the Council on Cardiovascular N. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation*. 122:406-41.

51. Miller WR, Rollnick, S. *Motivational interviewing: helping people change*. New York: The Guiford Press; 2013.

52. Deci EL RR. *Intrinsic motivation and self-determination in human behavior*. New York: Plenum; 1985.

53. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84:191-215.

54. Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process*. 1991;50:179-211.

55. Prochaska JO and Velicer WF. The transtheoretical model of health behavior change. *American Journal of Health Promotion*. 1997;12:38-48.

56. National Institute for Health and Care Excellence. 2018.

57. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, American College of Cardiology/American Heart Association Task Force on Practice G and Obesity S. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63:2985-3023.

58. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD and Wright JT, Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension (Dallas, Tex : 1979)*. 2017.

59. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ and Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810-52.

60. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Richard Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, Bart van der Worp H, van Dis I and Monique Verschuren WM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Rev Esp Cardiol (Engl Ed)*. 2016;69:939.

61. USDHHS. 2008 Physical Activity guidelines for Americans. 2008.

62. Thompson WG, N. Pescatello, L. American College of Sport's Medicine, Guidelines for Exercise Testing and Prescription. 2010.

63. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U, American Heart Association Physical Activity Committee of the Council on L, Cardiometabolic H, Council on Clinical C, Council on E, Prevention, Council on C, Stroke N, Council on Functional G, Translational B and Stroke C. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e653-e699.

64. Guazzi M, Labate V, Cahalin LP and Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction. *Eur J Prev Cardiol*. 2014;21:847-54.

65. Arena R, Myers J, Aslam SS, Varughese EB and Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J*. 2004;147:354-60.

66. Blair SN, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, Jr. and Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *Jama*. 1996;276:205-10.

67. Myers J, Prakash M, Froelicher V, Do D, Partington S and Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793-801.

68. Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC and Rankinen T. Genomic predictors of the maximal O(2) uptake response to standardized exercise training programs. *J Appl Physiol (1985)*. 2011;110:1160-70.

69. Ross R, de Lannoy L and Stotz PJ. Separate Effects of Intensity and Amount of Exercise on Interindividual Cardiorespiratory Fitness Response. *Mayo Clin Proc*. 2015;90:1506-14.

70. De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, Arena R and Milani RV. Cardiac Rehabilitation Fitness Changes and Subsequent Survival. *European heart journal Quality of care & clinical outcomes*. 2018.

71. Bakker EA, Snoek JA, Meindersma EP, Hopman MTE, Bellersen L, Verbeek ALM, Thijssen DHJ and Eijsvogels TMH. Absence of Fitness Improvement Is Associated with Outcomes in Heart Failure Patients. *Med Sci Sports Exerc*. 2018;50:196-203.

72. de Lannoy L, Clarke J, Stotz PJ and Ross R. Effects of intensity and amount of exercise on measures of insulin and glucose: Analysis of inter-individual variability. *Plos One*. 2017;12:e0177095.

73. Ross R, Hudson R, Day AG and Lam M. Dose-response effects of exercise on abdominal obesity and risk factors for cardiovascular disease in adults: study rationale, design and methods. *Contemp Clin Trials*. 2013;34:155-60.

74. Arena R, McNeil A, Street S, Bond S, Laddu DR, Lavie CJ and Hills AP. Let Us Talk About Moving: Reframing the Exercise and Physical Activity Discussion. *Current problems in cardiology*. 2018;43:154-179.

75. Arena R and McNeil A. Let's Talk about Moving: The Impact of Cardiorespiratory Fitness, Exercise, Steps and Sitting on Cardiovascular Risk. *Brazilian journal of cardiovascular surgery*. 2017;32:Iii-v.

76. Segar M, Taber JM, Patrick H, Thai CL and Oh A. Rethinking physical activity communication: using focus groups to understand women's goals, values, and beliefs to improve public health. *BMC Public Health*. 2017;17:462.

77. Segar ML, Guerin E, Phillips E and Fortier M. From a Vital Sign to Vitality: Selling Exercise So Patients Want to Buy It. *Curr Sports Med Rep*. 2016;15:276-81.

78. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, Milner J, Koh WP, Xie L, Zucker M, Buckley M, Cosgrove L, Lockett T, Fung KY and Head R. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *Journal of nutrigenetics and nutrigenomics*. 2011;4:69-89.

79. Masson LF, McNeill G and Avenell A. Genetic variation and the lipid response to dietary intervention: a systematic review. *The American journal of clinical nutrition*. 2003;77:1098-1111.

80. de Roos B. Personalised nutrition: ready for practice? *The Proceedings of the Nutrition Society*. 2013;72:48-52.

81. Wang DD and Hu FB. Precision nutrition for prevention and management of type 2 diabetes. *The lancet Diabetes & endocrinology*. 2018;6:416-426.

82. Fallaize R, Macready AL, Butler LT, Ellis JA and Lovegrove JA. An insight into the public acceptance of nutrigenomic-based personalised nutrition. *Nutrition research reviews*. 2013;26:39-48.

83. Minich DM and Bland JS. Personalized lifestyle medicine: relevance for nutrition and lifestyle recommendations. *TheScientificWorldJournal*. 2013;2013:129841.

84. Zeisel SH, Freake HC, Bauman DE, Bier DM, Burrin DG, German JB, Klein S, Marquis GS, Milner JA, Pelto GH and Rasmussen KM. The nutritional phenotype in the age of metabolomics. *The Journal of nutrition*. 2005;135:1613-6.

85. de Toro-Martin J, Arsenault BJ, Despres JP and Vohl MC. Precision Nutrition: A Review of Personalized Nutritional Approaches for the Prevention and Management of Metabolic Syndrome. *Nutrients*. 2017;9.

86. Radjursoga M, Karlsson GB, Lindqvist HM, Pedersen A, Persson C, Pinto RC, Ellegard L and Winkvist A. Metabolic profiles from two different breakfast meals characterized by (1)H NMR-based metabolomics. *Food chemistry*. 2017;231:267-274.

87. Garcia-Perez I, Posma JM, Gibson R, Chambers ES, Hansen TH, Vestergaard H, Hansen T, Beckmann M, Pedersen O, Elliott P, Stamler J, Nicholson JK, Draper J, Mathers JC, Holmes E and Frost G. Objective assessment of dietary patterns by use of metabolic phenotyping: a randomised, controlled, crossover trial. *The lancet Diabetes & endocrinology*. 2017;5:184-195.

88. Loo RL, Zou X, Appel LJ, Nicholson JK and Holmes E. Characterization of metabolic responses to healthy diets and association with blood pressure: application to the Optimal Macronutrient Intake Trial for Heart Health (OmniHeart), a randomized controlled study. *Am J Clin Nutr*. 2018;107:323-334.

89. Floegel A, Wientzek A, Bachlechner U, Jacobs S, Drogan D, Prehn C, Adamski J, Krumsiek J, Schulze MB, Pischon T and Boeing H. Linking diet, physical activity, cardiorespiratory fitness and obesity to serum metabolite networks: findings from a population-based study. *Int J Obes (Lond)*. 2014;38:1388-96.

90. Floegel A, Stefan N, Yu Z, Muhlenbruch K, Drogan D, Joost HG, Fritsche A, Haring HU, Hrabe de Angelis M, Peters A, Roden M, Prehn C, Wang-Sattler R, Illig T, Schulze MB, Adamski J, Boeing H and Pischon T. Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. *Diabetes*. 2013;62:639-48.

91. Magnusson M, Lewis GD, Ericson U, Orho-Melander M, Hedblad B, Engstrom G, Ostling G, Clish C, Wang TJ, Gerszten RE and Melander O. A diabetes-predictive amino acid score and future cardiovascular disease. *Eur Heart J*. 2013;34:1982-9.

92. Weng L, Quinlivan E, Gong Y, Beitelshees AL, Shahin MH, Turner ST, Chapman AB, Gums JG, Johnson JA, Frye RF, Garrett TJ and Cooper-DeHoff RM. Association of branched and aromatic amino acids levels with metabolic syndrome and impaired fasting glucose in hypertensive patients. *Metabolic syndrome and related disorders*. 2015;13:195-202.

93. Guasch-Ferre M, Hruby A, Toledo E, Clish CB, Martinez-Gonzalez MA, Salas-Salvado J and Hu FB. Metabolomics in Prediabetes and Diabetes: A Systematic Review and Meta-analysis. *Diabetes Care*. 2016;39:833-46.

94. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, Lewis GD, Fox CS, Jacques PF, Fernandez C, O'Donnell CJ, Carr SA, Mootha VK, Florez JC, Souza A, Melander O, Clish CB and Gerszten RE. Metabolite profiles and the risk of developing diabetes. *Nat Med*. 2011;17:448-53.

95. Kimberly WT, Wang Y, Pham L, Furie KL and Gerszten RE. Metabolite profiling identifies a branched chain amino acid signature in acute cardioembolic stroke. *Stroke*. 2013;44:1389-95.

96. Dietrich S, Floegel A, Weikert C, Prehn C, Adamski J, Pischon T, Boeing H and Drogan D. Identification of Serum Metabolites Associated With Incident Hypertension in the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. *Hypertension (Dallas, Tex : 1979)*. 2016;68:471-7.

97. Cui M, Wang Q and Chen G. Serum metabolomics analysis reveals changes in signaling lipids in breast cancer patients. *Biomedical chromatography : BMC*. 2016;30:42-7.

98. Moore SC, Playdon MC, Sampson JN, Hoover RN, Trabert B, Matthews CE and Ziegler RG. A Metabolomics Analysis of Body Mass Index and Postmenopausal Breast Cancer Risk. *Journal of the National Cancer Institute*. 2018.

99. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER and Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444:1027-31.

100. Guinane CM and Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. *Therapeutic advances in gastroenterology*. 2013;6:295-308.

101. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G and Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107:14691-6.

102. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman

FD and Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. *Science (New York, NY)*. 2011;334:105-8.

103. Floegel A, von Ruesten A, Drogan D, Schulze MB, Prehn C, Adamski J, Pischon T and Boeing H. Variation of serum metabolites related to habitual diet: a targeted metabolomic approach in EPIC-Potsdam. *Eur J Clin Nutr*. 2013;67:1100-8.

104. De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, Laghi L, Serrazanetti DI, Di Cagno R, Ferrocino I, Lazzi C, Turroni S, Cocolin L, Brigidi P, Neviani E, Gobbetti M, O'Toole PW and Ercolini D. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*. 2016;65:1812-1821.

105. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ and Hazen SL. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19:576-85.

106. Fraser GE. Vegetarian diets: what do we know of their effects on common chronic diseases? *Am J Clin Nutr*. 2009;89:1607s-1612s.

107. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA and Martinez-Gonzalez MA. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279-90.

108. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ and Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505:559-63.

109. Qi L. Gene-diet interaction and weight loss. *Current opinion in lipidology*. 2014;25:27-34.

110. Chaput JP, Doucet E and Tremblay A. Obesity: a disease or a biological adaptation? An update. *Obes Rev*. 2012;13:681-91.

111. Moreno-Aliaga MJ, Santos JL, Marti A and Martinez JA. Does weight loss prognosis depend on genetic make-up? *Obes Rev*. 2005;6:155-68.

112. Marti A, Martinez-Gonzalez MA and Martinez JA. Interaction between genes and lifestyle factors on obesity. *The Proceedings of the Nutrition Society*. 2008;67:1-8.

113. Deram S and Villares SM. Genetic variants influencing effectiveness of weight loss strategies. *Arquivos brasileiros de endocrinologia e metabologia*. 2009;53:129-38.

114. Bachlechner U, Floegel A, Steffen A, Prehn C, Adamski J, Pischon T and Boeing H. Associations of anthropometric markers with serum metabolites using a targeted metabolomics approach: results of the EPIC-potsdam study. *Nutrition & diabetes*. 2016;6:e215.

115. Rukh G, Sonestedt E, Melander O, Hedblad B, Wirfalt E, Ericson U and Orho-Melander M. Genetic susceptibility to obesity and diet intakes: association and interaction analyses in the Malmo Diet and Cancer Study. *Genes & nutrition*. 2013;8:535-47.

116. Goni L, Cuervo M, Milagro FI and Martinez JA. A genetic risk tool for obesity predisposition assessment and personalized nutrition implementation based on macronutrient intake. *Genes & nutrition*. 2015;10:445.

117. McCaffery JM, Papandonatos GD, Huggins GS, Peter I, Kahn SE, Knowler WC, Hudnall GE, Lipkin EW, Kitabchi AE, Wagenknecht LE and Wing RR. FTO predicts weight regain in the Look AHEAD clinical trial. *Int J Obes (Lond)*. 2013;37:1545-52.

118. Qi Q, Bray GA, Hu FB, Sacks FM and Qi L. Weight-loss diets modify glucose-dependent insulinotropic polypeptide receptor rs2287019 genotype effects on changes in body weight, fasting glucose, and insulin resistance: the Preventing Overweight Using Novel Dietary Strategies trial. *Am J Clin Nutr*. 2012;95:506-13.

119. Qi Q, Bray GA, Smith SR, Hu FB, Sacks FM and Qi L. Insulin receptor substrate 1 gene variation modifies insulin resistance response to weight-loss diets in a 2-year randomized trial: the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. *Circulation*. 2011;124:563-71.

120. Qi Q, Xu M, Wu H, Liang L, Champagne CM, Bray GA, Sacks FM and Qi L. IRS1 genotype modulates metabolic syndrome reversion in response to 2-year weight-loss diet intervention: the POUNDS LOST trial. *Diabetes Care*. 2013;36:3442-7.

121. Pan Q, Delahanty LM, Jablonski KA, Knowler WC, Kahn SE, Florez JC and Franks PW. Variation at the melanocortin 4 receptor gene and response to weight-loss interventions in the diabetes prevention program. *Obesity (Silver Spring)*. 2013;21:E520-6.

122. Larsen LH, Angquist L, Vimaleswaran KS, Hager J, Viguerie N, Loos RJ, Handjieva-Darlenska T, Jebb SA, Kunesova M, Larsen TM, Martinez JA, Papadaki A, Pfeiffer AF, van Baak MA, Sorensen T, Holst C, Langin D, Astrup A and Saris WH. Analyses of single nucleotide polymorphisms in selected nutrient-sensitive genes in weight-regain prevention: the DIOGENES study. *Am J Clin Nutr*. 2012;95:1254-60.

123. Heni M, Herzberg-Schafer S, Machicao F, Haring HU and Fritsche A. Dietary fiber intake modulates the association between variants in TCF7L2 and weight loss during a lifestyle intervention. *Diabetes Care*. 2012;35:e24.

124. Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA and Qi L. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. *Diabetes*. 2012;61:3005-11.

125. Kostis WJ, Cabrera J, Hooper WC, Whelton PK, Espeland MA, Cosgrove NM, Cheng JQ, Deng Y, De Staerck C, Pyle M, Maruthur N, Reyes I, Anderson CA, Liu J and Kostis JB. Relationships between selected gene polymorphisms and blood pressure sensitivity to weight loss in elderly persons with hypertension. *Hypertension (Dallas, Tex : 1979)*. 2013;61:857-63.

126. Erez G, Tirosh A, Rudich A, Meiner V, Schwarzfuchs D, Sharon N, Shpitzen S, Bluher M, Stumvoll M, Thiery J, Fiedler GM, Friedlander Y, Leiterstdorf E and Shai I. Phenotypic and genetic variation in leptin as determinants of weight regain. *Int J Obes (Lond)*. 2011;35:785-792.

127. Zhang X, Qi Q, Bray GA, Hu FB, Sacks FM and Qi L. APOA5 genotype modulates 2-y changes in lipid profile in response to weight-loss diet intervention: the Pounds Lost Trial. *Am J Clin Nutr*. 2012;96:917-22.

128. World Health Organization. WHO Report on the Global Tobacco Epidemic. 2013.

129. Centers for Disease Control and Prevention. Smoking & Tobacco Use: Fast Facts. 2018;2018.

130. Kelly MP, Barker, M. Why is changing health-related behaviour so difficult? *Public health*. 2016;136:109-116.

131. Weinstein ND. Accuracy of smokers' risk perceptions. *Annals of Behavioral Medicine*. 1998;20:135-140.

132. Hughes JR, Keely, J., Naud, S. Shape of the relapse curve and long- term abstinence among untreated smokers. *Addiction*. 2004;99:29-38.

133. Verbiest M, Brakema, E., van der Kleij, R., Sheals, K., Allistone, G., Williams, S., McEwen, A., Chavannes, N. National guidelines for smoking cessation in primary care: a literature review and evidence analysis. *NPJ Primary Care Respiratory Medicine*. 2017;27:2.

134. U.S. Department of Health and Human Services. Clinical Practice Guideline: Treating Tobacco Use and Dependence 2008 Update. 2008.

135. Britt E, Hudson, S.M., Blampied, N.M. Motivational interviewing in health settings: A review. *Patient education and counseling*. 2004;53:147-155.

136. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* . Arlington, VA: American Psychiatric Publishing; 2013.

137. Prochaska JO, Redding, C.A., Evers, K.E. The Transtheoretical Model and Stages of Change. In: K. Glanz, Rimer, B.K., Viswanath, K., ed. *Health Behavior and Health Education: Theory, Research, and Practice* San Francisco, CA: Jossey-Bass A Wiley Imprint; 2008: 97-145.

138. Cahill K, Lancaster, T., Green, N. Stage-based interventions for smoking cessation. *The Cochrane database of systematic reviews*. 2010;11:CD004492.

139. West R. Time for a change: putting the Transtheoretical (Stages of Change) Model to rest. *Addiction*. 2005;100:1036-1039.

140. Sheeran P, Klein, W. M., & Rothman, A. J. . Health behavior change: moving from observation to intervention. *Annual Review of Psychology*. 2017;68:573-600.

141. Rise J, Kovac, V., Kraft, P., & Moan, I. S. . Predicting the intention to quit smoking and quitting behaviour: Extending the theory of planned behaviour. *British Journal of Health Psychology*. 2008;13:291-310.

142. Gwaltney CJ, Metrik, J., Kahler, C. W., & Shiffman, S. . Self-efficacy and smoking cessation: a meta-analysis. *Psychology of Addictive Behaviors*. 2009;23:56.

143. Engels RC, Knibbe, R. A., de Vries, H., & Drop, M. J. . Antecedents of smoking cessation among adolescents: who is motivated to change? *Preventive medicine*. 1998;27:348-357.

144. Tate JC, & Stanton, A. L. . Assessment of the validity of the Reasons for Smoking scale *Addictive Behaviors*. 1990;15:129-135.

145. Villanti AC, Bover Manderski, M. T., Gundersen, D. A., Steinberg, M. B., & Delnevo, C. D. . Reasons to quit and barriers to quitting smoking in US young adults *Family Practice*. 2016;33:133-139.

146. Lundahl B, Moleni, T., Burke, B. L., Butters, R., Tollefson, D., Butler, C., & Rollnick, S. Motivational interviewing in medical care settings: A systematic review and meta-analysis of randomized controlled trials. *Patient education and counseling*. 2013;93:157-168.

147. Miller WR, Rollnick, S. *Motivational Interviewing: Helping People Change.* 3 ed. New York, NY: Guilford Press; 2013.

148. Weekley III CK, Klesges, R. C., & Reylea, G. . Smoking as a weight-control strategy and its relationship to smoking status. *Addictive Behaviors*. 1992;17:259-271.

149. Jeffery RW, Hennrikus, D. J., Lando, H. A., Murray, D. M., & Liu, J. W. . Reconciling conflicting findings regarding postcessation weight concerns and success in smoking cessation. *Health Psychology*. 2000;19:242.

150. Perkins KA, Marcus, M.D., Levine, M.D., D'amico, D., Miller, A., Broge, M., Ashcom, J., Shiffman, S. Cognitive-behavioral therapy to reduce weight concerns improves smoking cessation outcome in weight-concerned women. *Journal of Consulting and Clinical Psychology* 2001;69:604.

151. MacPherson L, Tull, M.T., Matusiewicz, A.K., Rodman, S., Strong, D.R., Kahler, C.W., Hopko, D.R., Zvolensky, M.J., Brown, R.A., & Lejuez, C.W.,. Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. *Journal of consulting and clinical psychology*. 2010;78:55-61.

152. McFall M, Saxon, A.J., Malte, C.A., Chow, B., Bailey, S., Baker, D.G., Beckham, J.C., Boardman, K.D., Carmody, T.P., Joseph, A.M., Smith, M.W.,. Integrating tobacco cessation into mental health care for posttraumatic stress disorder: a randomized controlled trial. *Jama*. 2010;304:2485-2493.

153. Hughes J. An algorithm for choosing among smoking cessation treatments. *Journal of Substance Abuse Treatment*. 2008;34:426-432.

154. Sampson L, Papadakos, J., Milne, V., Le, L.W., Liu, G., Abdelmutti, N., Milne, R., Goldstein, D.P., Eng, L. Giuliani, M. Preferences for the provision of smoking cessation education among cancer patients. *Journal of Cancer Education*. 2018;33:7-11.

155. Reid RD, Pritchard, G., Walker, K., Aitken, D., Mullen, K.A., Pipe, A.L.,. Managing smoking cessation. *Canadian Medical Association Journal*. 2016;188:E484-E492.

156. Chamberlain C, Perlen, S., Brennan, S., Rychetnik, L., Thomas, D., Maddox, R., Alam, N., Banks, E., Wilson, A., Eades, S., . Evidence for a comprehensive approach to Aboriginal tobacco control to maintain the decline in smoking: an overview of reviews among Indigenous peoples. *Systematic Reviews*. 2017;6:135.

157. Baezconde-Garbanati L, & Garbanati, J. A. . Tailoring tobacco control messages for Hispanic populations. *Tobacco Control*. 2000;9:i51.

158. Nollen N, Ahluwalia, J. S., Mayo, M. S., Richter, K., Choi, W. S., Okuyemi, K. S., & Resnicow, K. A randomized trial of targeted educational materials for smoking cessation in African Americans using transdermal nicotine. *Health Education & Behavior*. 2007;34:911-927.

159. Matthews AK, Sánchez-Johnsen, L., & King, A. Development of a culturally targeted smoking cessation intervention for African American smokers. *Journal of Community Health*. 2009;34:480.

160. Caraballo RS, Giovino, G.A., Pechacek, T.F., Mowery, P.D., Richter, P.A., Strauss, W.J., Sharp, D.J., Eriksen, M.P., Pirkle, J.L., Maurer, K.R. Racial and ethnic differences in serum cotinine levels of cigarette smokers: Third National Health and Nutrition Examination Survey, 1988-1991. *Jama*. 1998;280:135-139.

161. Bierut LJ, Johnson, E. O., & Saccone, N. L. A glimpse into the future–Personalized medicine for smoking cessation. *Neuropharmacology*. 2014;76:592-599.

162. Spohr SA, Nandy, R., Gandhiraj, D., Vemulapalli, A., Anne, S., & Walters, S. T. . Efficacy of SMS text message interventions for smoking cessation: a meta-analysis. *Journal of Substance Abuse Treatment*. 2015;56.

163. Naughton F. Delivering "Just-In-Time" smoking cessation support via mobile phones: Current knowledge and future directions. *Nicotine & Tobacco Research* 2017;19:379-383.

164. Hébert ET, Stevens, E.M., Frank, S.G., Kendzor, D.E., Wetter, D.W., Zvolensky, M.J., Buckner, J.D., Businelle, M.S. An ecological momentary intervention for smoking cessation: The associations of just-in-time, tailored messages with lapse risk factors. *Addictive Behaviors*. 2018;78:30-35.

165. National Academies of Sciences E, and Medicine. National Academies of Sciences, Engineering, and Medicine: Advancing obesity solutions through investments in the built environment: Proceedings of a workshop—in brief. 2017.

166. Sallis JF and Glanz K. Physical activity and food environments: solutions to the obesity epidemic. *The Milbank quarterly*. 2009;87:123-54.

167. Board TR. Does the built environment influence physical activity? Examining the evidence: TRB Special Report 282. 2005.

168. Medicine Io. Accelerating progress in obesity prevention: Solving the weight of the nation. 2012.

169. Organization WH. Physical Inactivity: A Global Public Health Problem. 2015.

170. Bull F. Monitoring Global Progress of Physical Activity: The Role and Progress of Civil Society in Holding Governments to Account. *Journal of physical activity & health*. 2015;12:1195-7.

171. Giles-Corti B, Vernez-Moudon A, Reis R, Turrell G, Dannenberg AL, Badland H, Foster S, Lowe M, Sallis JF, Stevenson M and Owen N. City planning and population health: a global challenge. *Lancet*. 2016;388:2912-2924.

172. Ewing R and Cervero R. Travel and the Built Environment. *Journal of the American Planning Association*. 2010;76:265-294.

173. Sallis JF, Bull F, Burdett R, Frank LD, Griffiths P, Giles-Corti B and Stevenson M. Use of science to guide city planning policy and practice: how to achieve healthy and sustainable future cities. *Lancet*. 2016;388:2936-2947.

174. Kim S-H and Willis LA. Talking about obesity: News framing of who is responsible for causing and fixing the problem. *Journal of health communication*. 2007;12:359-376.

175. Pearl RL and Lebowitz MS. Beyond personal responsibility: Effects of causal attributions for overweight and obesity on weight-related beliefs, stigma, and policy support. *Psychology & health*. 2014;29:1176-1191.

176. Barry CL, Brescoll VL and Gollust SE. Framing childhood obesity: How individualizing the problem affects public support for. *Political Psychology*. 2013;34:327-349.

177. Wakefield MA, Loken B and Hornik RC. Use of mass media campaigns to change health behavior. *The Lancet*. 2010;376:1261-1271.

178. Kornfield R, Szczypka G, Powell LM and Emery SL. Televised obesity-prevention advertising across US media markets: exposure and content, 2010–2011. *Public health nutrition*. 2015;18:983-993.

179. Welch Cline RJ. Everyday interpersonal communication and health. *Routledge handbook of health communication*. 2011;2nd:377-398.

180. Smith A and Anderson M. Social Media Use in 2018. 2018;2018.

181. Abril EP, Szczypka G and Emery SL. LMFAO! Humor as a Response to Fear: Decomposing Fear Control within the Extended Parallel Process Model. *Journal of Broadcasting and Electronic Media*. 2017;61.

182. Emery SL, Szczypka G, Abril EP, Kim Y and Vera L. Are you scared yet? Evaluating fear appeal messages in Tweets about the Tips campaign. *Journal of Communication*. 2014;64:278-295.

183. Vaterlaus JM, Patten EV, Roche C and Young JA. #Gettinghealthy: The perceived influence of social media on young adult health behaviors. *Computers in Human Behavior*. 2015;45:151-157.

184. Abril EP and O'Connell C. Our daily communicative contexts. An application of the communication mediation model to healthy foods consumption. 2018.

185. Franklin NC, Lavie CJ and Arena RA. Personal health technology: A new era in cardiovascular disease prevention. *Postgrad Med*. 2015;127:150-8.

186. van den Brekel-Dijkstra K, Rengers AH, Niessen MA, de Wit NJ and Kraaijenhagen RA. Personalized prevention approach with use of a web-based cardiovascular risk assessment with tailored lifestyle follow-up in primary care practice--a pilot study. *Eur J Prev Cardiol*. 2016;23:544-51.

187. Piette JD, List J, Rana GK, Townsend W, Striplin D and Heisler M. Mobile Health Devices as Tools for Worldwide Cardiovascular Risk Reduction and Disease Management. *Circulation*. 2015;132:2012-27.

188. Pratt M, Sarmiento OL, Montes F, Ogilvie D, Marcus BH, Perez LG and Brownson RC. The implications of megatrends in information and communication technology and transportation for changes in global physical activity. *Lancet*. 2012;380:282-93.

189. Castro Sweet CM, Chiguluri V, Gumpina R, Abbott P, Madero EN, Payne M, Happe L, Matanich R, Renda A and Prewitt T. Outcomes of a Digital Health Program With Human Coaching for Diabetes Risk Reduction in a Medicare Population. *Journal of aging and health*. 2017:898264316688791.

190. WHO. mHealth: New horizons for health through mobile technologies. 2011.

191. Muralidharan S, Ranjani H, Anjana RM, Allender S and Mohan V. Mobile Health Technology in the Prevention and Management of Type 2 Diabetes. *Indian journal of endocrinology and metabolism*. 2017;21:334-340.

192. Haymes LK, Storey K, Maldonado A, Post M and Montgomery J. Using applied behavior analysis and smart technology for meeting the health needs of individuals with intellectual disabilities. *Developmental neurorehabilitation*. 2015;18:407-19.

193. Hassoon A, Schrack J, Naiman D, Lansey D, Baig Y, Stearns V, Celentano D, Martin S and Appel L. Increasing Physical Activity Amongst Overweight and Obese Cancer Survivors Using an Alexa-Based Intelligent Agent for Patient Coaching: Protocol for the Physical Activity by Technology Help (PATH) Trial. *JMIR Res Protoc*. 2018;7:e27.

194. Bickmore TW, Schulman D and Sidner C. Automated interventions for multiple health behaviors using conversational agents. *Patient education and counseling*. 2013;92:142-8.

195. Stein N and Brooks K. A Fully Automated Conversational Artificial Intelligence for Weight Loss: Longitudinal Observational Study Among Overweight and Obese Adults. *JMIR Diabetes*. 2017;2:e28.

196. Mák E, Pintér B, Gaál B, Vassányi I, Kozmann G and Németh I. A Formal Domain Model for Dietary and Physical Activity Counseling. 2010:607-616.

197. Liu Y, Wang H, Zhao W, Zhang M, Qin H and Xie Y. Flexible, Stretchable Sensors for Wearable Health Monitoring: Sensing Mechanisms, Materials, Fabrication Strategies and Features. *Sensors (Basel, Switzerland)*. 2018;18.

198. Chakravarti A. Genomics is not enough. *Science (New York, NY)*. 2011;334:15.

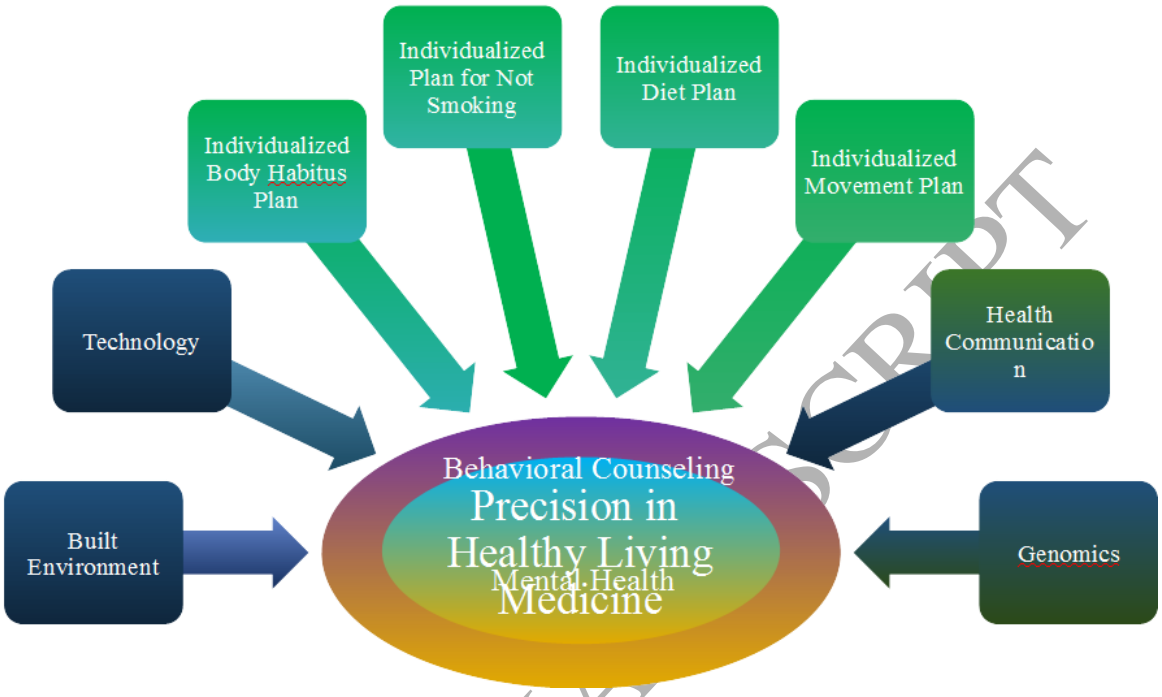
199. Cloud AJ, Thai A, Liao Y and Terry MB. The impact of cancer prevention guideline adherence on overall mortality in a high-risk cohort of women from the New York site of the Breast Cancer Family Registry. *Breast cancer research and treatment*. 2015;149:537-46.

200. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M and Tuomilehto J. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care*. 2003;26:3230-6.

201. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA and Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.

202. Antman EM and Loscalzo J. Precision medicine in cardiology. *Nat Rev Cardiol*. 2016;13:591-602.

Figure 1: Key Treatment and Supportive Components for Precision in Healthy Living Medicine



Legend:

Treatment Components

Supportive Components