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Furthering Precision Medicine Genomics With Healthy Living Medicine

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ABSTRACT

The Precision Medicine Initiative seeks to develop new approaches for disease treatment and prevention that considers the individual variation in genes, environment, and lifestyle for each person. To date, the focus has been on genetic drivers of disease risk and development but has now begun to incorporate lifestyle induced changes in phenotype to enhance treatments. Healthy Living Medicine is an emerging paradigm that focuses on moving more and sitting less, consuming a healthy diet, maintaining body weight and not smoking. A wealth of clinical trials has demonstrated the protective effects of high cardiorespiratory fitness, physical activity (PA), and exercise on all-cause mortality, and prevention of developing cardiovascular disease (CVD), obesity and type 2 diabetes (T2D). This review will summarize the impact of PA and exercise on modifying risk of disease from genetics in the general population and those with CVD, obesity and T2D.

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The National Research Council laid the initial framework for Precision Medicine in 2011 and was utilized by President Obama to institute the Precision Medicine Initiative in 2015. The goal of the initiative is to develop new approaches for disease treatment and prevention that considers "individual variability in genes, environment, and lifestyle for each person". Since the mapping of the human genome in 2003, precision medicine has been largely focused on genetic variability and associations with various diseases. However, genomic studies have

Abbreviations and acronyms: ACLS, Aerobics Center Longitudinal Study; AHEAD, Action for Health in Diabetes; BMI, body mass index; CHD, coronary heart disease; CR, cardiac rehabilitation; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; DPP, diabetes prevention program; DYRK1B, dual specificity tyrosine phosphorylated regulated kinase 1B; EHR, electronic health records; HbA1c, glycosylated hemoglobin; GWAS, genome wide association studies; HERITAGE, Health, Risk factors, exercise Training, And, Genetics; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HL, healthy living; HLM, healthy living medicine; LDLR, large deletion in the LDL receptor; LRP6, LDLR-related protein 6; MET, metabolic equivalent; MoTrPAC, Molecular Transducers of Physical Activity; MPVA, moderate to vigorous physical activity; PA, physical activity; PCI, percutaneous coronary intervention; QoL, quality of life; RCT, randomized controlled trials; SNPs, single nucleotide polymorphisms; T2D, type 2 diabetes; WGS, whole-genome sequencing.

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limitations in that they only measure a fraction of the genome, and do not account for interactions with other genes, proteins, and environment.[1] Additionally, environmental factors, such as components of healthy living (HL), can modify disease risk even when genetic variations are present.[2–5]

Healthy living medicine (HLM) is an emerging paradigm that describes 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.[6,7] Adhering to HLM has been shown to be effective at preventing or delaying the majority of chronic diseases, such as type 2 diabetes (T2D), cardiovascular disease (CVD), coronary heart disease (CHD) and cancer, resulting in an extended health span.[8] HLM will further the Precision Medicine Initiative by combining genomics with detailed physiological phenotyping of lifestyle, social and physical environment, and responses to exercise. Developing in-depth phenotypes of individuals allows for the classification of patients into new subpopulations. These subpopulations would differ with respect to the susceptibility of disease, phenotypic or molecular subclass of disease, or adverse response to a specific therapy.[9] Ultimately, the development of highly individualized phenotypes will lead to more accurate diagnoses, more rational prevention strategies, better treatment selection, and the development of novel therapies.[10]

The refocus of Precision Medicine to include the influence of HLM is due to the wealth of epidemiological and randomized control trials (RCTs) describing the benefits of HLM on overall health and disease risk. Importantly, individuals adhering to HLM with a genetic predisposition for developing disease reduced their risk of developing T2D[3,4] and CHD,[2] and improved cancer mortality rates.[5] Technological advances making 'omics' approaches more widely available have expanded the number of studies investigating biomarkers and molecular signatures that confer the beneficial effects of HLM on a molecular level. Combining genetic risk with deep phenotyping following HLM interventions will expand our understanding of the mechanisms involved in how HLM confer their benefits to the individual and further Precision Medicine. Due to the increasing recognition of the importance of physical activity (PA) and exercise on overall health, this review will focus on how PA and exercise impact Precision Medicine and risk for disease development and progression. Specifically, we will review the epidemiological studies, and RCTs describing the influence and beneficial effects of PA and exercise and their impact on disease risk and mortality in healthy individuals and those with CVD/CHD, and obesity and T2D.

Healthy living medicine for the general public

One of the challenges of the Precision Medicine Initiative is defining what is considered "normal or healthy". Particularly, estimating the normal range of variation across the population while taking into consideration other factors, such as race, age, gender and socioeconomic status.[11] These limitations can be overcome initially by linking longitudinal outcomes at the individual level and sharing large 'omic' data sets across laboratories and institutions which can form the basis for a normal phenotype.[11] Defining a normal phenotype is important for several reasons: 1) identify pathways and molecules that are associated with a healthy phenotype throughout the lifespan; 2) utilize the healthy phenotype to compare disease states for target identification for new therapeutic strategies; and 3) distinguish the interplay between genetic risk and environmental factors such as diet and exercise to the whole-body phenotype.

Physical activity is associated with overall health

The first PA guidelines for Americans were released in 2008. The primary guidance for adults is to perform a certain amount of moderate to vigorous PA (MVPA - 150 moderate-intensity, or 75 vigorous-intensity exercise every week) for health benefits including 2 days of muscle strengthening activity.[12] A new update to these guidelines has recently been released and while the primary MVPA recommendations remained the same more focus has been put on decreasing sedentary time and increasing time being active at any intensity.[13] These changes are a result of ten years of research investigating the health benefits of PA over the continuum, ranging from extremely sedentary/inactive to very active, of activity levels.

The 2008 guidelines are supported by a strong base of literature totaling 73 studies recommending 450–900 metabolic equivalent (MET) min/week.[12] At this activity level, the overall relative risk of death was reduced 31% after adjusting for potential confounders and was similar between men and women, and older adults. The 150 min recommendation of MVPA weekly was based on the observation that 2–2.5 h of MVPA was the minimum amount of activity to reduce all-cause mortality. However, when examining the exercise dose response from 11 large epidemiological studies, the 2–2.5 h dose of exercise does not represent a significant inflection point in the exercise dose/mortality curve.[14] Interestingly, the greatest reduction in mortality occurs at the lowest end of the exercise dose spectrum. A sedentary lifestyle compared to performing just 1.5 h MVPA is associated with a 20% risk reduction in mortality and to gain an additional 20% reduction another 5.5 h of MVPA is needed.[14] These findings highlight that any increase in PA from a sedentary lifestyle will result in a risk reduction in mortality. While any dose of exercise appears to be beneficial, an optimal minimum dose or maximum dose of exercise has not been determined.

The new exercise guidelines do not modify the current recommendations of 150 min/week of MVPA but highlight the importance of moving more and decreasing sedentary time.[13] These recommendations are supported by smaller studies showing a decrease in all-cause mortality with 1–1.9 h/week of moderate to vigorous exercise,[15] ≤1 h walking or cycling/week, and exercising less than once per week decreased mortality risk by 28%.[16] These findings have been now confirmed in large prospective cohort studies. Arem et al. found small amounts of exercise (0.1–7.5 MET-h/week) decreased mortality risk by 20% compared to sedentary participants.[17] This study also examined the influence of activity levels at the current guidelines (7.5–15 MET-h) and levels 3 to 5 times greater than the recommendations (27.5–45 MET-h) and found an additional 9% reduction in risk at each level conferring 39% risk reduction at the highest PA levels.[17] A study of Taiwanese adults who exercised at levels below the current guidelines (4.5 MET-h or 90 min/week MVPA) had a 14% reduction in mortality risk and improved life expectancy of 3 years.[18] Collectively, these studies highlight that while 150 min MVPA/week supports optimal health, lower amounts of exercise confer a significant benefit to overall health.

A wealth of evidence now exists indicating performing some MVPA can confer benefits and reduce all-cause mortality risk. The reduction in overall risk has been expanded by several studies showing PA participation is associated with the prevention of 25 chronic medical conditions.[19] Specifically, systematic reviews have revealed the average risk reduction of 20–30% for chronic medical conditions such as CVD, stroke, hypertension, cancer, and T2D, in individuals who were regularly active.[19] Similar to reductions in all-cause mortality risk, bouts of PA that are lower than the recommended 150 min/week MVPA still confer a reduction in disease risk. Wen et al. found 15 min/day or 90 min/week of MVPA reduced the risk of death from all causes by 15% as well as from cancers, CVD, and T2D.[18] Furthermore, every additional 15 min/day of PA up to 100 min/day provided an additional risk reduction of 4% for all-cause and 1% for all-cancer mortality.[18] Sattelmair et al. conducted a meta-analysis and found individuals exercising at half of the current PA recommendations showed a 14% lower risk of CHD.[20] The author's go further to comment that the greatest reductions in risk occur at the lower end of the activity spectrum.[20] The strength of PA with disease risk and mortality is improved further by an additional 20–30% when objective measures of aerobic fitness or cardiorespiratory fitness (CRF) are assessed and related to morbidity.[19] Collectively, PA and CRF are significant mediators of disease risk and adding CRF measurements to mediate disease risk

highlights the potential to use CRF as a biomarker for modifying disease risk in healthy sedentary individuals.

CRF as a biomarker for HLM

The Aerobics Center Longitudinal Study (ACLS) was the first prospective study to describe the connection between CRF and mortality. In a group of 10,224 men and 3120 women followed over 8 years an inverse relationship between CRF and all-cause mortality was found independently for sex, cardiovascular and CVD risk factors (age, blood cholesterol and pressure, obesity, smoking status family history, blood glucose and T2D).[21] The men and women with the highest CRF level had a 43% and 53% lower risk for all-cause mortality and 47% and 70% lower risk of CVD mortality, respectively.[21] These initial relationships were confirmed by a meta-analysis containing 33 investigations that included 102,980 healthy men and women. Kodama et al. found higher CRF was associated with lower all-cause and CHD/CVD mortality.[22] The authors expanded upon these associations in a dose-response relationship and found each 1-MET increment increase in CRF was associated with 13% and 15% risk reductions from all-cause mortality and CVD events, respectively.[22] This small increase in PA level may have significant clinical implications as a 1-MET higher level of aerobic capacity is comparable to a 7-mm reduction of waist circumference,[23] 5-mm Hg decrease in systolic blood pressure,[24] 1-mmol/L decrease in triglycerides (in men)[25] and plasma glucose,[26] and 8 mg/dL increment in high-density lipoprotein cholesterol.[27] These cross-sectional relationships have been validated in several longitudinal studies with multiple tests of CRF over time. Blair et al. followed 9777 men who had CRF tested twice over an average of 4.9 years. These men were followed for an average of 5.1 years for mortality.[28] The authors found the men who were unfit at both visits had the highest death risk, men who were fit at both visits had the lowest death risk, and men who changed CRF status (fit to unfit or unfit to fit) had intermediate risk.[28] Erikssen et al. followed 2014 healthy men and found improvements in CRF over a period of 7 years associated with a lower risk of all-cause mortality during 15 years of follow-up regardless of baseline CRF and changes in body weight.[29] Collectively, these data indicate that CRF is a very strong predictor of disease risk and mortality. This is likely due to CRF assessment requiring integration of multiple organ/body systems working together to circulate and extract oxygen, carbon dioxide, and nutrients to and from metabolically active tissues.

CRF is a surrogate measure of the functional ability of the respiratory, cardiovascular and musculoskeletal systems. CRF is determined by non-modifiable factors (age, gender and genotype) and modifiable factors, such as the tenants of HLM, PA, smoking, obesity and/or medical conditions. Improvements in CRF in response to exercise training can be variable, thus creating individuals who can be classified as "responders" and "non-responders".[30] There have been limited number of studies investigating the impact of genetics on CRF. The Health, Risk factors, exercise Training, And, Genetics (HERITAGE) family study has provided the strongest evidence of how much of the response to CRF after an exercise training program is related to genetics. A group of 473 Caucasian adults from 99 nuclear families completed 20 weeks of moderate intensity continuous training and had a 15–18% increase in CRF.[31] However, there was 2.5 times more variability between families than within families in CRF response and the maximal heritability estimate of the CRF response to training was 47%.[31] While genetics confer a significant portion of CRF response to exercise training, our understanding of the specific genes involved in mediating this response is limited.

Since the HERATIGE study, the Human Genome project was completed and spurred numerous investigations into understanding the role of genetic variations on health. A recent review by Williams et al. compiled 35 studies that have reported 97 genes associated with exercise induced training improvements in CRF.[30] Of the 97 genes, only a small number were identified across several studies highlighting the complexity of the exercise-related phenotype and relying on one variant may not be as effective as using multiple variants. Several investigations have used a "total genotype score" ranging from 0 to 100, where 0 is the worst and 100 being the best genotype combinations.[32,33] These scores are developed with algorithms and provide the opportunity to combine with other phenotypic data to provide more power to the determination of the cellular mechanisms underlying CRF and CRF trainability. A recent investigation has examined if the addition of routine and advanced clinical data with whole-genome sequencing (WGS) would improve disease risk detection and strengthen WGS variant interpretation. Perkins et al. enrolled 209 active, symptom free adults and conducted a personal and family medical history, WGS, whole-body magnetic resonance imaging, dual energy X-ray absorptiometry, global metabolomics, blood test for pre-diabetes, echocardiography, electrocardiography, and cardiac rhythm on each participant.[34] WGS alone identified possible age-related chronic disease associated with all-cause mortality, neoplasms, CVD, T2D, liver diseases, and neurologic disorders, while combining advanced imaging and other clinical data strengthened guideline driven WGS variant interpretation.[34] Interestingly, WGS was useful in explaining past medical history and possible future individual disease risk and the advanced imaging and other testing were more useful for detection of active disease.[34] While components of HLM were not measured, this investigation shows the effectiveness of combining both phenotypic and genomic data together and begins to highlight the potential for the tenants of HLM, PA and exercise, to serve as perturbations to identify key genetic variants and biomarkers associated with disease and disease risk.

Healthy living medicine in cardiovascular disease

In spite of the advances in our understanding and treatment, CVD remains the leading cause of death in developed countries.[35] CVD risk is influenced by multiple factors including genetics and lifestyle. As genetic risk is pre-defined, increasing emphasis is being placed on a healthy lifestyle. HLM incorporates multiple components of a healthy lifestyle including increased PA and exercise, healthy diet, maintaining healthy body weight, and no smoking. Adherence to these basic components has a significant impact on CVD morbidity and mortality.[36] Of these components, many studies have now shown quite convincingly a relationship between PA, CRF, and CVD risk. We will discuss the evidence for reduced CVD risk with increased PA, the use of exercise as a therapy following myocardial infarction or therapeutic interventions, and the relationship between HLM and genetic risk for CVD.

Physical activity and CVD risk and prevention

As described above, the current PA and exercise guidelines recommend 150 min moderate-intensity, or 75 min vigorous-intensity exercise every week.[13] This corresponds to approximately 7.5 metabolic-equivalent hours per week (MET-h/week). The benefits of this exercise include a reduction in all-cause mortality, maintaining a healthy weight, reduced fracture risk, and improved CRF and muscle fitness. These benefits obviously include multiple components of HLM as discussed above. There now exist many studies confirming the link between PA and exercise with a lower CVD risk. Early epidemiologic studies indicated that PA was related to CVD risk. The British Transport Workers study compared employees of the London Transport Executive that worked in jobs with relatively low PA, e.g. bus drivers, and high PA, e.g. conductors.[37,38] The rate of CHD in the conductors was found to be lower than the drivers giving some of the first indication that PA was directly linked to CVD risk. The Harvard Alumni Study surveyed male alumni from Harvard University for levels of light sports, strenuous sports, stairs climbed, and blocks walked per day. Even among participants with multiple CHD risk factors, those that expended >4200 kJ/-week had a lower CVD risk than those that expended <4200 kJ/week.[39] The Copenhagen City Heart study examined the relationship between long-term physical activity and death rates. Long-

term moderate or high levels of PA were associated with a reduction in all-cause mortality and CHD deaths.[40] Similar findings were also observed with cycling or even light jogging 2–3 times per week.[41,42] There is also a dose-response relationship between the amount of PA and exercise and reduction in CVD risk and all-cause mortality. One study examined MET-h/week of PA across 6 prospective cohort studies in the National Cancer Institute Cohort Consortium. This study found a dose-response increase in life expectancy up to 30 MET-h/week including among those individuals with CVD.[43] A similar analysis of this data revealed a reduction in CVD death was observed with a maximal benefit at around 22.5–40 MET-h/week or 3–5 times the recommended amount of PA.[17] However, it is important to note that a reduction in all-cause mortality and CVD death was observed from 0 to 7.5 MET-h/week, less than the recommended amount. This suggests that any amount of exercise above a completely sedentary lifestyle confers benefit.

However, the studies cited above demonstrate that PA is associated with a reduced CVD risk but do not necessarily establish a causal relationship. For instance, regardless of the level of PA, CRF has been shown to be an independent predictor of CVD risk. For instance, CRF and adiposity is an independent predictor of cardiometabolic risk in the Norwegian Generation 100 Study.[44] Similar findings were observed in the ACLS discussed above. In this study, men with diabetes with low fitness as quantified by a treadmill test had higher CVD death rates.[45] Other retrospective studies have confirmed a link between CRF and all-cause and CVD events.[22] In addition to CRF, hand grip strength is also correlated with all-cause and CVD-mortality.[46] Preclinical models also demonstrate an association between CRF and mortality. For instance, rats bred for inherent high CRF (under non-exercised conditions) show greater longevity than those with low CRF.[47] However, no increase in longevity was observed when the high or low CRF rats were subjected voluntary to wheel running.[48] Discordant exercise activity also explains mortality differences in dizygotic but not monozygotic twins.[48] These provocative data suggest that genetic predisposition influences PA levels and that intrinsic CRF is a better predictor of CVD risk and all-cause mortality. Large randomized exercise intervention trials would be needed to definitively determine this.

Cardiac rehabilitation as a therapeutic intervention

Although much of the focus, understandably, is on prevention of CVD, there is an important role for a healthy lifestyle in patients following a CHD event. Cardiac rehabilitation (CR) is now prescribed for patients of various forms of CVD or events, such as myocardial infarction, coronary stent placement and stable heart failure (HF) with reduced ejection fraction (HFrEF).[49] CR incorporates many aspects of the healthy lifestyle with exercise or PA being central in addition to nutritional and smoking cessation interventions. Importantly, the exercise component is physician-directed and medically supervised with a very low incidence of CVD events.[50] The HF-ACTION trial is the largest study to date that has examined the safety and efficacy of exercise in over 2300 patients with HFrEF.[51] The study examined the effects of a combination of walking, treadmill and stationary bike exercise at prescribed percentages of maximal heart rate five times per week. The results of HF-ACTION demonstrated non-significant reductions in CVD mortality or HF hospitalization in those patients prescribed exercise as compared to the usual care group. However, these findings were significant when adjusted for baseline characteristics. Importantly, there were significant improvements in physical fitness and 6-minute walk test that indicate improvements in quality of life (QoL).[52] In addition, a retrospective analysis of several studies in patients with HF with preserved systolic function (HFpEF) has shown improvements in CRF and QoL that were not associated with changes in either diastolic or systolic function.[53] This suggests that exercise-mediated improvements in these patients may not be due to primary effects on cardiac function but rather peripheral effects on skeletal muscle, endothelial function or arterial stiffness (affecting peripheral vascular resistance). These results underscore that assessment of the type of exercise most beneficial in both HFpEF and HFrEF cohorts is warranted.

CR is not limited to HF patients as it has been shown to benefit patients following percutaneous coronary intervention (PCI). For instance, one study examined the Veteran's Affairs database for patients undergoing CR following PCI. In spite of the relatively low participation, PCI patients participating in a CR program had a 33% lower mortality rate at a 6-year follow-up period as compared to non-participants.[54] In addition, those patients attending the most CR sessions (36 or more) had the lowest mortality rate underscoring the importance of continued participation. An analysis of Medicare beneficiaries hospitalized for CHD conditions or revascularization procedures also demonstrated significantly lower mortality rates in participants of CR programs as compared to nonparticipants.[55] Taken together, these studies firmly establish CR as an evidence-based therapeutic strategy for CVD patients. CR encompasses many of the aspects of HLM concept and should be incorporated into common practice in the treatment of CVD.

Genetic risk factors for CVD and HLM

The occurrence and pathogenesis of CHD is influenced by a complex interplay of genetics and lifestyle. The risk of developing CHD increases when there are first-degree relatives with the disease.[56,57] It is estimated that heritability accounts for >40% of the risk of developing CHD.[58] Early studies into genetic determinants of CHD focused on family-based studies. For instance, a ground-breaking study of familial hypercholesterolemia identified a large deletion in the LDL receptor (*LDLR*) gene.[59] Other genes such as the LDLR-related protein 6 (*LRP6*) and dual specificity tyrosine phosphorylated regulated kinase 1B (*DYRK1B*) have been identified by similar approaches.[60,61] Although these studies have been successful in the identification of genes associated with CHD risk, these variants are relatively rare and have a large individual contribution to CHD risk. These also require the identification of afflicted families to uncover these genetic origins. Other studies with large numbers have examined more common variants in genome wide association studies (GWAS). GWAS are designed to identify more common variants of at least 0.5% frequency. Together, approximately 60 genetic loci have been identified through these approaches.[62] One particular power of these studies is that collectively, these loci can be grouped in biologic processes that contribute to CHD and CVD risk, including lipoprotein (LDL cholesterol and triglyceride-rich particles), inflammation, vascular remodeling and hypertension.[62] However, the relationship of many of the variants and genes identified to CHD and CVD risk remains unknown.

Adherence to a healthy lifestyle including non-smoking, healthy diet and exercise is known to decrease CVD risk. For instance, the Nurse's Healthy Study demonstrated that middle aged women adhering to a healthy lifestyle had an approximate 80% lower incidence of CHD events as compared to the population as a whole.[63] A similar study in Swedish men found almost the exact reduction in CVD risk with a healthy lifestyle.[64] However, given the strong heritability of CVD, what impact does healthy lifestyle has on those individuals with a high genetic risk? In other words, can one mitigate high genetic risk with adoption of a healthy lifestyle? A number of studies have addressed this question. A meta-analysis of multiple cohorts generated a genetic risk score based on over 49,000 single nucleotide polymorphisms (SNPs).[65] In this analysis, non-smoking, low cholesterol, and low blood pressure – factors all associated with a healthy lifestyle – attenuated CVD risk in those with a high genetic risk score. Finally, in a seminal study by Kathiresan et al. examined the interaction between genetic risk score and a healthy lifestyle in over 55,000 participants across 4 studies.[5] The genetic risk score was calculated by using 50 SNPs identified and validated in previous studies. The highest quintile had a >90% CVD risk as compared to the lowest quintile. However, adherence to a healthy lifestyle reduced risk for coronary events in all groups including the highest risk group by nearly 50%. These results demonstrate that a healthy lifestyle reduces

CVD risk independently of genetic risk and should be recommended to all persons. In addition, these studies collectively stress the importance of a healthy diet and weight, exercise, and abstinence from smoking for those individuals at high genetic risk for CVD. These data also underscore that risk for CHD events and CVD can be mitigated by personal lifestyle choices and not "pre-determined". Finally, incorporation of testing for known and well-validated genetic markers for high risk patients should be considered.

Healthy living medicine in obesity and type 2 diabetes

Obesity and T2D rates have escalated significantly over the last 3 decades. The World Health Organization reported 600 million adults were classified as obese in 2014[66] and the number of individuals with T2D was 415 million in 2015 and is expected to increase to 642 million by 2040.[67] These increases in prevalence bring huge economic burden as the cost of T2D management in 2017 was estimated to be $US850 billion and is expected to increase to $US958 billion by 2045.[68] It is no surprise that obesity[69] and diabetes[70] are associated with increase in premature mortality. Additionally, obesity and T2D are associated with the development of CVD, hypertension, dyslipidemia and hyperglycemia.[68,71] HLM tenants, PA, exercise and diet, along with medications are the first line of treatment for these metabolic disorders. We will discuss the evidence for reduced risk of obesity and T2D with increased PA, the use of exercise as a therapy for obesity and T2D, and the relationship between HLM and genetic risk for obesity and T2D. When appropriate obesity and T2D will be discussed separately.

Physical activity and obesity and T2D risk and prevention

Obesity is classified using body mass index (BMI) and has several grades. Grade 1 obesity is a BMI 30–34.9 kg/m^2, grade 2: 35–39.9 kg/m^2, grade 3: ≥40 kg/m^2, grade 4: ≥50 kg/m^2 and grade 5: ≥60 kg/m^2.[71] Overall, obesity is associated with an increased mortality rate,[72] however a recent meta-analysis including 2.88 million individuals found the specific grade of obesity impacts risk. Flegal et al. found increased mortality rate (hazard ratio of 1.18) when all obesity grades were combined, however grade 1 obesity was not associated with increased mortality risk (hazard ratio of 0.97) and only severe obesity (grade 2 or 3) was associated with an increased mortality risk (hazard ratio of 1.34).[73] These data highlight the need for interventions to prevent individuals from progressing to the severe grades of obesity and developing T2D and other co-morbidities.

Lifestyle interventions utilizing a combination of exercise and diet are commonly the first treatment option for obesity and T2D. Several prospective observational studies in women and men have consistently shown a reduction in the incidence of T2D among physically active individuals compared to sedentary peers with only 30 min/day of moderate-intensity activity. In the Nurses' Health study, 70,000 healthy US women aged 40–65 years walked briskly for at least 2.5 h/week (30 min/day, 5 days/week). This activity was associated with a 25% reduction in diabetes over 8 years of follow-up even after adjusting for age, BMI and other risk factors for T2D.[74] The Women's Health study found similar benefits after a 6.9-year follow-up. Nearly 38,000 health professionals in the US aged 45 years and older who reported walking 2–3 h/week were 34% less likely to develop diabetes compared to those who reported they did not walk.[75] Similar findings have been described in cohorts of men. The Kuipio Ischemic Heart Disease Risk Factor study followed 897 Finnish men aged 42–60 years for 4.2 years. Those who performed at least 40 min/week of leisure time PA >5.5 METS were 56% less likely to develop T2D than men who did not after adjusting for BMI and other covariates.[76] The Health Professionals Follow-up study following ~38,000 men in the US aged 40–75 years for 10 years and found each 10 MET/h increment in weekly walking energy expenditure was associated with an 11% reduction in T2D risk.[77] Collectively, these studies describe a significant reduction of risk in developing T2D with only a small amount of daily exercise. These beneficial effects of PA have also been shown to be effective for individuals who are already obese and/or have T2D.

The American Heart Association, American College of Cardiology, and Obesity Society suggest intensive lifestyle intervention goals should be 5%–10% weight-loss over 6 months.[78] Additionally, once initial weight-loss is achieved, continued participation in the weight-loss program is needed for 1 or more years for long-term weight maintenance.[78] The US Diabetes Prevention Program (DPP) study is the longest and largest RCT to investigate the effects of weight-loss achieved by diet and exercise on individuals with risk to develop T2D. Knowler et al. randomized 3234 men and women (51 years, BMI: 34 kg/m^2) with elevated fasting and postload glucose to a lifestyle modification program with the goal of ≥7% weight-loss and ≥150 min/week of exercise, metformin only (850 mg twice daily), or placebo.[4] The diet and exercise and metformin groups had a reduction in T2D risk of 58% and 31% compared to placebo, respectively.[4] These findings were replicated by the Finnish Diabetes Trial. Tuomilehto et al. randomized 522 men and women (55 years, BMI: 31 kg/m^2) to a diet and exercise program with a goal to achieve ≥5% weight-loss and perform ≥30 min/day moderate-intensity exercise or control.[79] They also found a 58% reduction in T2D risk compared to control.[79] The Look AHEAD (Action for Health in Diabetes) trial examined the effects of weight-loss with lifestyle intervention in patients with well-established T2D. A total of 5145 overweight or obese adults (45–74 years) were randomized to lifestyle intervention or a control group. After 1 year, the lifestyle intervention group had greater weight-loss (8.6% vs. 0.7%) and reductions in glycosylated hemoglobin (HbA1c) (7.3% to 6.6% vs. 7.3 to 7.2%), improved CRF level, and decreased risk factors.[80] These three investigations describe a potent effect of lifestyle interventions including exercise to reduce T2D risk in individuals who are obese and at risk for developing or have T2D. Another important factor some of these studies have addressed is the maintenance of weight-loss and disease risk once the clinical trial is completed.

The DPP study conducted a 10-year follow-up study to examine the impact of the lifestyle intervention or metformin on the risk for T2D. The metformin group maintained weight-loss while the lifestyle intervention group regained the weight and both groups maintained an 18% and 34% reduced T2D incidence, respectively.[81] The Finnish Diabetes study had some individuals who participated in the lifestyle program that did not achieve the 5% weight-loss but did complete the exercise program. Although these individuals did not lose weight, performing the exercise program reduced their diabetes risk by 20% compared to their counterparts who maintained a sedentary lifestyle.[79] These data highlight the beneficial and lasting effects of exercise on T2D risk, even without weight-loss. However, it is recommended that higher levels of PA are needed for long-term maintenance of the health benefits of exercise.[82]

Genetic risk factors for obesity and T2D

The genetic component to the occurrence and pathogenesis of obesity and T2D is a complex interplay between genetics and lifestyle. It is estimated that the heritability of BMI is 30–40%[83] and the risk of a child developing obesity increases 2.5 fold to 4.0 fold if one parent is obese and 10 fold if both parents are obese compared with having both parents of normal weight.[84] Risk of transmission of T2D is also well documented. The Framingham Offspring study found the odds ratio for offspring to have T2D were 3.5 or 3.4 if the father or mother has T2D, respectively and 6.1 if both parents have T2D.[85] The elevated risk of developing these metabolic disorders has led to several studies seeking to identify the potential underlying genetic mechanisms responsible for conferring this risk.

There have been several GWAS studies that have identified nearly 150 genetic variants associated with BMI, waist circumference or obesity risk in multiple populations.[86,87] The most studied SNP has been the *FTO* gene as it is associated with the development of obesity[88] and

T2D.[89] Frayling et al. found individuals who are homozygous for the *FTO* risk allele weighed 3 kg more and had a 1.67-fold increased odds of obesity when compared to those not inheriting a risk allele.[90] Since 2007, *FTO* has been associated with obesity in European, African-American, Hispanic, Pacific Islander and East Asian populations.[91] These associations led researchers to investigate whether there is an interaction between lifestyle modifications and *FTO* variation that may reduce risk of developing disease. An analysis of the DPP study, discussed above, found no evidence that *FTO* modified the effects of lifestyle intervention on weight-loss, but may impact subcutaneous adipose mass.[92] Similarly, a meta-analysis of clinical trial data found no evidence of an interaction between *FTO* and lifestyle.[93] Another clinical trial analysis combined data from the DPP and the Look AHEAD trial and again confirmed no associations with *FTO*, however identified lifestyle-gene interactions with the *MTIF3* gene.[94] *MTIF3* is essential for ATP synthesis and energy balance in the mitochondria.[95] These data support the potential for genes to impact risk for obesity and T2D. However, of the variants currently identified, only ~3% explain the variance in BMI, suggesting a large number of variants remain unidentified.[86] In efforts to explain the missing heritability in obesity and T2D, researchers have turned to epigenetics.

Epigenetics is defined as changes in gene transcription and expression that do not involve changes to the underlying DNA sequence. Epigenetic modifications include DNA methylation, histone post-translational modifications and chromatin remodeling or inheritance of mRNAs that regulate gene expression.[96] Dicks et al. analyzed 450 million CpG sites in two cohorts and found an association between BMI and DNA methylation at the *HIF3α* locus.[97] Wahl et al. found associations with BMI and changes in DNA methylation in 187 loci involved in lipid metabolism and insulin resistance.[98] Despite these associations, replication of these findings in other studies has been problematic and there are few RCTs to examine and confirm the importance of these sites. Ronn et al. examined the impact of <6-month exercise intervention on DNA methylation patterns and their association with obesity.[99] Exercise altered genes associated with obesity and adipogenesis, *FTO GRB14*, and *TUB*, in adipose tissue and these changes were associated with decreased waist-circumference in middle-aged men.[99] The LIPOGAIN trial examined the effects of two types of high-energy content muffin supplementation for 7 weeks in conjunction with normal diet on methylation marks in abdominal subcutaneous adipose tissue in young adults (21–38 years). Three genes, carbonic anhydrase 3, connective tissue growth factor, and aldehyde dehydrogenase 1 family member A1, were differentially expressed suggesting modification by the diet.[100] Collectively, understanding the impact of genetics and epigenetics on obesity and T2D has shown promise. However, the lack of understanding thus far is likely due to the multifactorial nature of obesity and T2D having large influences of an individual's environment and genetics.

Precision medicine may be able to enhance our understanding of the risk of developing obesity and T2D by utilizing clinical phenotypes to establish more granular definitions or subtypes of disease. Ahlqvist et al. used machine learning algorithms to assess six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and HOMA2 estimates of β-cell function and insulin resistance) from 8980 Swedish patients with newly diagnosed diabetes and developed 5 subtypes of diabetes.[101] Each cluster was characterized by certain phenotypic features that classified patients in the following groupings: early-onset severe autoimmune disease (6.7% of patients), severe insulin-deficient diabetes (17.5% of patients), mild obesity related diabetes (21.6% of patients), and mild age-related diabetes (39.1% of patients).[101] While this approach is not without limitations,[102] classifying patients into more descriptive diagnoses may help identify the genetic influence of disease rather than grouping individuals under one umbrella of diagnosis.

Conclusions and future directions

We have reviewed the influence of PA and exercise on mitigating an individual's risk for developing disease and improving health outcomes in those with CVD, obesity and T2D. Additionally, we highlight the limitations of genetics to completely explain the risk of disease and identify those who are at risk for disease development. The tenants of HLM, specifically PA and exercise, have a dramatic effect on disease prevention and progression for those with disease. The integration of phenotypic data following HLM with genomics provides a stronger framework for the Precision Medicine Initiative to achieve the goal of merging the participant, health care practitioner, and research into an individual-level relationship focused on the prevention and treatment of common diseases (Fig. 1).

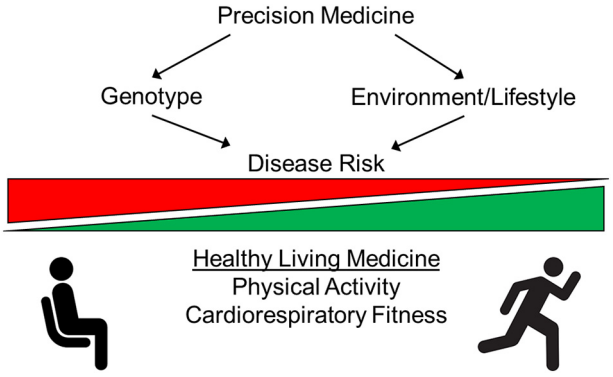

Fig. 1. The Precision Medicine Initiative seeks to combine both genetics, environment, and lifestyle of an individual to enhance the treatment for and prediction of developing disease. Tenants of Health Living Medicine (HLM), such as physical activity and exercise, are potent at preventing disease development and can improve disease outcomes for those with disease. Performing regular PA and exercise, and maintaining a high cardiorespiratory fitness (CRF) dramatically reduces an individual's mortality rate and risk for developing diseases. Additionally, PA and exercise can prevent disease progression and improve health outcomes in those who have disease.

The incorporation of phenotypic data, such as electronic health records (EHR), into databases for genomics research have grown and involve several countries including the US, Iceland, UK and China.[103] Utilizing EHR allows researchers easier access to large amounts of patient data over time and reduces the cost of performing the research. A recent analysis compared the cost of 115 previously conducted pharmacogenetic studies with the cost of 28 EHR-based pharmacogenetic studies and found the EHR-based approach reduced study costs by 82% per subjects (US$478 to $96) and took a shorter time to complete.[103] These innovative practices will enhance genetic research and accelerate Precision Medicine. There are also many Precision Medicine Initiatives specific to T2D,[102] and several associated with HLM. The National Institutes of Health Common Fund Initiative on Molecular Transducers of Physical Activity (MoTrPAC) seeks to understand the health benefits of exercise and molecular determinants that confer those benefits,[104] and the Food4Me study founded by the European Union examined the role of genetics in the personalization of diet.[105] Collectively, these initiatives will have great impact on our understanding of genetics and human health and disease.

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