

Review Article

The integrated effect of moderate exercise on coronary heart disease

Marc J Mathews, Edward H Mathews, George E Mathews

Abstract

Background: Moderate exercise is associated with a lower risk for coronary heart disease (CHD). A suitable integrated model of the CHD pathogenetic pathways relevant to moderate exercise may help to elucidate this association. Such a model is currently not available in the literature.

Methods: An integrated model of CHD was developed and used to investigate pathogenetic pathways of importance between exercise and CHD. Using biomarker relative-risk data, the pathogenetic effects are representable as measurable effects based on changes in biomarkers.

Results: The integrated model provides insight into higher-order interactions underlying the associations between CHD and moderate exercise. A novel 'connection graph' was developed, which simplifies these interactions. It quantitatively illustrates the relationship between moderate exercise and various serological biomarkers of CHD. The connection graph of moderate exercise elucidates all the possible integrated actions through which risk reduction may occur.

Conclusion: An integrated model of CHD provides a summary of the effects of moderate exercise on CHD. It also shows the importance of each CHD pathway that moderate exercise influences. The CHD risk-reducing effects of exercise appear to be primarily driven by decreased inflammation and altered metabolism.

Keywords: moderate exercise, biomarkers, integrated model

Submitted 11/9/15, accepted 5/5/16

Published online 12/12/16

Cardiovasc J Afr 2017; 28: 125–133

www.cvja.co.za

DOI: 10.5830/CVJA-2016-058

Coronary heart disease (CHD) is known to be the major cause of death globally.¹ However, it is well documented that regular moderate physical exercise is associated with fewer CHD events in symptomatic² and asymptomatic^{3,4} subjects. The precise mechanisms underlying this inverse association

are unclear. However, it is apparent that CHD risk may be substantially mediated, through moderate exercise, by changes in blood pressure, insulin resistance and glucose intolerance, systemic inflammation, triglyceride concentrations, low high-density lipoprotein (HDL) levels and obesity.^{4,5}

It may therefore prove beneficial to quantify and elucidate the underlying pathogenetic effect of moderate exercise on the pathogenesis of CHD. Using a previously described integrated model of CHD,^{6,7} we investigated the interconnectivity of moderate exercise and the pathogenesis and pathophysiological attributed to CHD.

Methods

An integrated model was developed as part of a larger research project.⁶ This project has partially been described in previous articles dealing with certain subsets of the research.^{7,9} Briefly, a systematic review of the literature post-1998 and including highly cited articles was conducted for CHD pathogenesis, health factors, biomarkers and pharmacotherapeutics. This research was combined to develop the integrated model of CHD.

During the systematic literature review, PubMed, Science Direct, Ebsco Host and Google Scholar were searched for publications with 'coronary heart disease' or 'coronary artery disease' or 'cardiovascular disease' or 'CHD' as a keyword and combinations with 'lifestyle effects', 'relative risk prediction', 'network analysis', 'pathway analysis', 'interconnections', 'systems biology', 'pathogenesis', 'biomarkers', 'conventional biomarkers', 'drugs', 'therapeutics', 'pharmacotherapeutics', 'hypercoagulability', 'hypercholesterolaemia', 'hyperglycaemia', 'hyperinsulinaemia', 'inflammation' and 'hypertension' in the title of the study.

Also searched were all major relevant speciality journals in the areas of cardiology, alcohol consumption, nutrition, cigarette smoking, physical exercise, oral health, psychological stress, depression, sleep disorders, endocrinology, psychoneuro-endocrinology, systems biology, physiology, periodontology, CHD, the metabolic syndrome and diabetes.

The health factors in the integrated model were considered as lifestyle effects or co-morbid health disorders that have been associated with statistically significant increases or decreases in CHD risk. This resulted in nine health factors being considered in the model, namely alcohol, food, exercise, smoking, oral health, stress, depression, insomnia and sleep apnoea.

The biomarkers considered for the integrated model were mainly those whose measurement has been associated with statistically significant increases or decreases in CHD risk.

Centre for Research and Continued Engineering Development,
North-West University, Potchefstroom, South Africa

Marc J Mathews, PhD

Edward H Mathews, PhD

George E Mathews, 20270046@nwu.ac.za

This resulted in 23 biomarkers being considered in the model, namely triglycerides, low-density lipoprotein (LDL), HDL, apolipoprotein-B (Apo B), leptin, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), growth-differentiation factor-15 (GDF-15), osteoprotegerin (OPG), myeloperoxidase (MPO), B-type natriuretic peptide (BNP), homocysteine, fibrinogen, troponins, urinary albumin-to-creatinine ratio (ACR), glycosylated haemoglobin (HbA_{1c}), insulin-like growth factor-1 (IGF-1), adiponectin, cortisol, brain-derived neurotrophic factor (BDNF) and insulin resistance.

In brief, the systematic review of the literature revealed the pathological effects of various health factors on the pathogenesis of CHD. This information was combined to form a visual representation of the pathogenesis of CHD as it is affected by these health factors. The biomarkers were included in the visual representation to show functionally measurable aspects of the pathogenesis.^{6,7} This visual representation presents an integrated model of CHD.

This integrated model of CHD schematically illustrates the complexity of CHD and shows all theoretical pathogenetic pathways between health factors and CHD. The model has been previously used to describe the effects of high-carbohydrate diets on CHD,⁷ and the possible mechanisms through which antidepressants⁹ and moderate alcohol consumption⁸ may reduce CHD risk.

In this study the integrated model was used to describe the integrated effects of exercise on the pathogenesis of CHD. Furthermore, the effect of exercise on CHD was investigated by analysing the effect that exercise has been shown to have on measurable and quantifiable biomarkers.

Statistical analysis



It must be noted that some of the relative risk (RR) values in this article differ from convention. The need for this comes as a result of the visual scaling of the traditional RR. Traditionally, if one plots an RR = 3 and RR = 0.33, respectively, one does not 'look' three times worse and the other three times better than the normal RR = 1. The reason is that the scales for the positive and negative effects are not numerically similar. A graph of 'good' and 'bad' RR can therefore be deceptive for the untrained person, for example a patient.

This article rather uses the method that the conventional RR = 3 is three times worse than the normal RR = 1, while the conventional RR = 0.33 means that the patient's position is three times better than the normal RR = 1. Therefore, in summary, a conventional RR = 3 is presented as per normal, as a three-fold increase in risk and a conventional RR = 0.33 is presented as a three-fold decrease in risk ($1/0.33 = 3$).

Results

Integrated model of coronary heart disease

The integrated model of CHD that was developed in previous studies is presented in Fig. 1. The pathways (pathogenesis of CHD) within the integrated model can be tracked from where a chosen health factor influences the relevant tissue, to the end state of CHD. The pathways are therefore a visual representation of previously published knowledge. Salient serological biomarkers

(shown in Fig. 1 as ) and pharmacotherapeutics (shown in Fig. 1 as ) that act on the pathways are further indicated in Fig. 1.

The focus of this review is on using the integrated model to describe the interconnections of moderate exercise on the pathogenesis of CHD. Therefore a more detailed discussion of Fig. 1, relevant to exercise, is given in the next section. This review therefore attempts to quantify the CHD effect of moderate exercise by the connection of these to an array of biomarkers that represent increasing or decreasing CHD risk.

Pathogenetic effects of physical exercise

In order to appraise the CHD effects of moderate exercise, the relevant pathogenetic pathways need to be considered. While Fig. 1 also indicates other health factors, only the pathways activated by moderate exercise are summarised in Table 1. It is however important to note that not all the pathways will be relevant to every patient and that all the pathways may not be active simultaneously, or occur in the same patient.

Fig. 1 (pathway: 3a-53-55-hyperglycaemia) shows the pathways involved in a lack of physical exercise (and decreased daily energy expenditure) and how this affects carbohydrate metabolism through changes in muscle glucose transporter

Table 1. Putative effects of moderate exercise and salient CHD pathogenetic pathways

| Pathways, and pathway numbers corresponding to those in Fig. 1 | References |
|---|----------------------|
| a. 3a-53- \downarrow blood glucose-55- \downarrow hyperglycaemia | 38, 39 |
| b. 3a-53- \downarrow blood glucose-54- \downarrow PI3K:MAPK-69- \downarrow insulin resistance-72- \downarrow platelet factors-73- \downarrow hypercoagulability | 40-47 |
| c. 3a-53- \downarrow blood glucose-54- \downarrow PI3K:MAPK-69- \downarrow insulin resistance-72- \downarrow ROS | 38, 40, 45-48 |
| d. 3a-53- \downarrow blood glucose-54-28-101- \downarrow insulin resistance-72- \uparrow vasodilation | 49 |
| e. 3b-27- \downarrow cortisol-47- \downarrow insulin resistance-70- \downarrow angiotensin II-89- \downarrow hypertension-100- \downarrow ROS-85- \downarrow COX1/2-85- \downarrow inflammatory state | 29, 30, 38, 45, 48 |
| f. 3b-27- \downarrow cortisol-47- \downarrow insulin resistance-70- \downarrow angiotensin II-89- \downarrow SMC proliferation | 50 |
| g. 3b-27- \downarrow cortisol-47- \downarrow insulin resistance-70- \downarrow angiotensin II-89- \uparrow IGF1-84- \downarrow SMC proliferation | 51-54 |
| h. 3b-27- \downarrow cortisol-47- \downarrow insulin resistance-70- \downarrow angiotensin II-89- \downarrow VCAM1/MCP1-73- \downarrow hypercoagulation | 29 |
| i. 3c- \downarrow visceral adipose tissue- \downarrow ectopic fat | 38, 55, 56 |
| j. 3c-19- \uparrow adiponectin-38- \downarrow TNF α /IL6-56-Liver-12- \downarrow LDL-33- \downarrow oxLDL-51- \downarrow hypercholesterolaemia | 38, 56, 57 |
| k. 3c-19- \uparrow adiponectin-39- \downarrow insulin resistance | 58 |
| l. 3c-19- \uparrow adiponectin-39- \downarrow SMC proliferation | 55 |
| m. 3c-21- \downarrow TNF α /IL6-56-Liver-12- \downarrow LDL-33- \downarrow oxLDL-51- \downarrow hypercholesterolaemia | 5, 32, 59-62 |
| n. 3c-21- \downarrow TNF α /IL6-41- \downarrow P. gingivalis-43- \downarrow periodontitis-64- \downarrow platelet factors-73- \downarrow hypercoagulability | 5, 32, 59-62 |
| o. 3c-18- \downarrow FFA-37- \downarrow plasma lipids-34-Liver-12- \downarrow LDL-33- \downarrow oxLDL-51- \downarrow hypercholesterolaemia | 5, 32, 38, 56, 59-62 |

\uparrow , up regulation/increase; \downarrow , down regulation/decrease; x-y-z indicates pathway connecting x to y to z. FFA, free fatty acids; IGF 1, insulin-like growth factor-1; IL6, interleukin-6; LDL, low-density lipoprotein; MAPK, mitogen-activated protein (MAP) kinase; MCP 1, monocyte chemo-attractant protein-1; NO, nitric oxide; oxLDL, oxidised LDL; P. gingivalis, Porphyromonas gingivalis; PI3K, phosphatidylinositol 3-kinase; PI3K:MAPK, ratio of PI3K to MAPK; ROS, reactive oxygen species; SMC, smooth muscle cell; TNF α , tumour necrosis factor- α ; VCAM 1, vascular cell adhesion molecule-1.

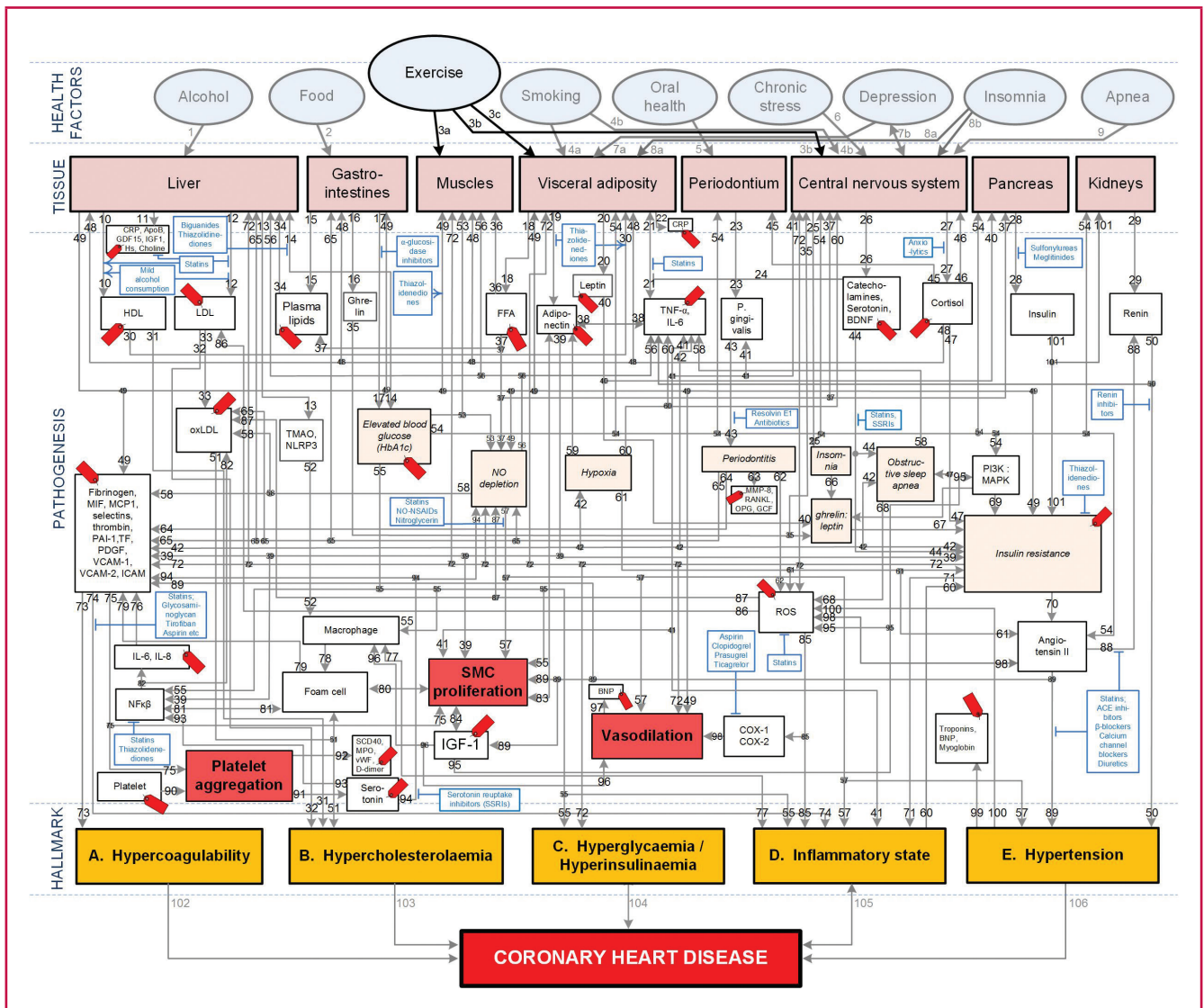


Fig. 1. Conceptual model of general health factors, salient CHD pathogenetic pathways and CHD hallmarks. (From: M Mathews, L Liebenberg, E Mathews. How do high glyceric load diets influence coronary heart disease? *Nutr Metab* 2015; 12(1): 6.) The affective pathway of pharmacotherapeutics (blue boxes) is shown in Fig. 1, and salient serological biomarkers are indicated by the tags (). The blunted arrows denote antagonise or inhibit, and pointed arrows denote up-regulate or facilitate. ACE, angiotensin converting enzyme; BDNF, brain-derived neurotrophic factor; β -blocker, beta-adrenergic antagonists; BNP, B-type natriuretic peptide; COX, cyclooxygenase; CRP, C-reactive protein; D-dimer, fibrin degradation product D; FFA, free fatty acids; GCF, gingival crevicular fluid; HbA_{1c}, glycosylated haemoglobin A_{1c}; HDL, high-density lipoprotein; Hs, homocysteine; ICAM, intracellular adhesion molecule; IGF-1, insulin-like growth factor-1; IL, interleukin; LDL, low-density lipoprotein; MAPK, mitogen-activated protein (MAP) kinase; MCP, monocyte chemo-attractant protein; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NF κ β , nuclear factor- κ B; NLRP3, Inflammasome responsible for activation of inflammatory processes as well as epithelial cell regeneration and microflora; NO, nitric oxide; NO-NSAIDs, combinational NO-non-steroidal anti-inflammatory drug; OPG, osteoprotegerin; oxLDL, oxidised LDL; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; *P. gingivalis*, *Porphyromonas gingivalis*; PI3K, phosphatidylinositol 3-kinase; RANKL, receptor activator of nuclear factor kappa-beta ligand; ROS, reactive oxygen species; SCD-40, recombinant human sCD40 ligand; SMC, smooth muscle cell; SSRI, serotonin reuptake inhibitors; TF, tissue factor; TMAO, an oxidation product of trimethylamine (TMA); TNF- α , tumour necrosis factor- α ; VCAM, vascular cell adhesion molecule; VWF, von Willebrand factor.

(GLUT) protein content. Denervation of skeletal muscle results in rapid decreases in both muscle GLUT-4 contents and insulin-stimulated glucose uptake, therefore resulting in hyperglycaemia and concomitant hyperinsulinaemia (both CHD hallmarks) in non-diabetic patients.¹⁰

Lack of physical exercise may also contribute to the accumulation of visceral fat, reduced lipoprotein lipase activity and reduced clearance of triglycerides, leading to increased LDL levels, decreased HDL levels, and increased LDL-to-HDL ratios, and eventually to hypercholesterolaemia.¹¹ This state

subsequently activates the oxidative stress/inflammation cascade. This in turn underlies insulin resistance and the evolution of micro- and macrovascular complications (Fig. 1, pathways: 3a-53-blood glucose-54-PI3K:MAPK-69-insulin resistance-72-ROS). Hyperinsulinaemia, by itself, contributes significantly to atherogenicity, leading to CHD.¹²

An increase in plasma free fatty acid (FFA) concentrations plays a key role in the pathogenesis of insulin resistance through actions that block insulin signal transduction. An increase in FFA levels results in induction of oxidative stress, low-grade systemic inflammation, and subnormal vascular reactivity, in addition to causing insulin resistance.⁵ As insulin resistance also results in the relative non-suppression of adipocyte hormone-sensitive lipase,¹³ there is further enhancement in lipolysis, increased FFA and insulin resistance. As insulin suppresses pro-inflammatory transcription factors, such as nuclear factor- κ B (NF- κ B), and also suppresses reactive oxygen species (ROS) generation, insulin resistance therefore also has a comprehensive pro-inflammatory effect (Fig. 1, pathways: 3c-18-FFA-37-plasma lipids-34-12-LDL-33-oxLDL-51-hypercholesterolaemia).

Fig. 1 therefore shows why an insulin-resistant state may be pro-inflammatory. The origin of the insulin resistance may be traced back to the pro-inflammatory cytokine TNF- α , which is expressed by adipose tissue.¹⁴ Adipose tissue has been shown to express not only TNF- α , but also other pro-inflammatory mediators, including CRP. Macrophages residing in the adipose tissue may also be a source of pro-inflammatory factors and they can also modulate the secretory activities of adipocytes¹⁵ (Fig. 1, pathway: 3c-21-TNF α /IL6).

During regular moderate exercise, IL-6 is produced by skeletal muscle fibres via a TNF-independent pathway. IL-6 stimulates the appearance in the circulation of anti-inflammatory cytokines, which inhibit the production of pro-inflammatory TNF- α .¹⁶ Additionally, IL-6 enhances lipid turnover, stimulating lipolysis as well as fat oxidation. Regular physical exercise therefore induces suppression of TNF- α and thereby offers protection against TNF- α -induced insulin resistance.¹⁶ Low-grade systemic inflammation therefore appears to be aetiologically linked to the pathogenesis of CHD,¹⁷ countered by moderate exercise with its anti-inflammatory effects⁵ (Fig. 1, pathway: 3a-53-blood glucose-54-69-insulin resistance-71).

The adipokine adiponectin is anti-inflammatory and potentially anti-atherogenic.⁵ Low adiponectin levels act as a marker for CHD and are associated with overweight subjects.¹⁸ Regular physical exercise (and an energy-controlled diet) reduces visceral fat mass, with a subsequent increased release of anti-inflammatory adiponectin, therefore resulting in reduced risk of CHD¹⁹ (Fig. 1, pathway: 3c-19-39-insulin resistance).

Lack of physical exercise may lead to hypertension, another CHD hallmark, through increased vascular and sympathetic tone created by reduced bioavailability of nitrous oxide (NO) and activation of the renin-angiotensin system^{20, 21} (Fig. 1, pathway: 3a-53-blood glucose-54-60-72-vasodilation). Hypertension is directly correlated with visceral fat mass, which may be decreased by moderate exercise.²²

The lower blood glucose levels that result from moderate exercise lead to a reduction in the phosphatidylinositol 3-kinase (PI3K) to mitogen-activated protein kinase (MAPK) ratio, which in turn decreases insulin resistance²³ (Fig. 1, pathway: 3a-53-blood glucose-54-69-72-73-hypercoagulability). Increased

insulin sensitivity decreases serum levels of platelet factors and thus reduces the potential for hypercoagulability.^{24,25}

Moderate exercise also increases coronary blood flow,²⁶ which increases the release of prostaglandins.²⁷ This is important in heart microvasculature, in which prostaglandins are substantially involved in flow-mediated vasodilation.²⁷

Moderate exercise acts on the central nervous system by decreasing serum cortisol levels.²⁸ This in turn reduces insulin resistance, which decreases angiotensin II levels and results in reduced hypertension. Reactive oxygen species (ROS) and cyclooxygenase (COX) 1/2 levels reduce concomitantly, which lead to a lower inflammatory state²⁰ (Fig. 1, pathway: insulin resistance-85-inflammatory state).

It is apparent that moderate exercise directly and indirectly affects a plethora of interconnected pathogenetic mechanisms. Each CHD hallmark and pathogenetic trait can amplify the

Table 2. Association between biomarkers and prediction of CHD relative risk

| Biomarker (class and salient examples) | Prediction of CHD relative risk (95% CI) | Size of studies (N = number of trials, n = number of patients) | Refer- ences |
|---|--|--|-----------------|
| Lipid-related markers | | | |
| Triglycerides | 0.99 (0.94–1.05) | (N = 68, n = 302 430) | 63 |
| LDL | 1.25 (1.18–1.33) | (N = 15, n = 233 455) | 64 |
| HDL | 0.78 (0.74–0.82) | (N = 68, n = 302 430) | 63 |
| Apo B | 1.43 (1.35–1.51) | (N = 15, n = 233 455) | 64 |
| Leptin | 1.04 (0.92–1.17) | (n = 1 832) | 65 |
| Inflammatory markers | | | |
| hsCRP | 1.20 (1.18–1.22) | (N = 38, n = 166 596) | 66 |
| IL-6 | 1.25 (1.19–1.32) | (N = 25, n = 42 123) | 67 |
| TNF- α | 1.17 (1.09–1.25) | (N = 7, n = 6 107) | 67 |
| GDF-15 | 1.40 (1.10–1.80) | (n = 1 740) | 68 |
| OPG | 1.41 (1.33–1.57) | (n = 5 863) | 69 |
| Marker of oxidative stress | | | |
| MPO | 1.17 (1.06–1.30) | (n = 2 861) | 70 |
| Marker of vascular function and neurohormonal activity | | | |
| BNP | 1.42 (1.24–1.63) | (N = 40, n = 87 474) | 71 |
| Homocysteine | 1.15 (1.09–1.22) | (N = 20, n = 22 652) | 72, 73 |
| Coagulation marker | | | |
| Fibrinogen | 1.15 (1.13–1.17) | (N = 40, n = 185 892) | 66 |
| Necrosis marker | | | |
| Troponins | 1.15 (1.04–1.27) | (n = 3 265) | 58 |
| Renal function marker | | | |
| Urinary ACR | 1.57 (1.26–1.95) | (n = 626) | 74 |
| Metabolic markers | | | |
| HbA _{1c} | 1.42 (1.16–1.74) | (N = 2, n = 2 442) | 75 |
| IGF-1 | 0.76 (0.56–1.04) | (n = 3 967) | 76 |
| Adiponectin | 0.97 (0.86–1.09) | (N = 14, n = 21 272) | 77 |
| Cortisol | 1.10 (0.97–1.25) | (n = 2 512) | 78, 79 |
| BDNF | ? | ? | 80–82 |
| Insulin resistance (HOMA) | 1.46 (1.26–1.69) | (N = 17, n = 51 161) | 83 |

From: M Mathews, L Liebenberg, E Mathews. How do high glycemic load diets influence coronary heart disease? *Nutr Metab* 2015; **12**(1): 6.⁷
n, number of participants; *N*, number of trials; CI, confidence interval; ACR, albumin-to-creatinine ratio; Apo B, apolipoprotein-B; BDNF, brain-derived neurotrophic factor; BNP, B-type natriuretic peptide; GDF-15, growth-differentiation factor-15; HbA_{1c}, glycated haemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; hsCRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LDL, low-density lipoprotein; MPO, myeloperoxidase; OPG, osteoprotegerin; TNF- α , tumour necrosis factor- α .



Fig. 2. Normalised relative risks (fold-change) of salient current biomarkers or of potential serological biomarkers for CHD. (From: M Mathews, L Liebenberg, E Mathews. How do high glycemic load diets influence coronary heart disease? *Nutr Metab* 2015; 12(1): 6.) Increased IGF-1 and HDL levels are associated with a moderately decreased CHD risk. (IGF-1 and HDL levels are significantly inversely correlated to relative risk for CHD.) *N* indicates number of trials; I, 95% confidence interval; ACR, albumin-to-creatinine ratio; Adipo, adiponectin; ApoB, apolipoprotein-B; BDNF, brain-derived neurotrophic factor; BNP, B-type natriuretic peptide; Cort, cortisol; CRP, C-reactive protein; cysteine, homocysteine; fibrin, fibrinogen; GDF-15, growth-differentiation factor-15; HbA_{1c}, glycosylated haemoglobin A_{1c}; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LDL, low-density lipoprotein; MPO, myeloperoxidase; OPG, osteoprotegerin; TNF-α, tumour necrosis factor-α; Trlg, triglycerides; Trop, troponins.

patient’s risk of CHD, therefore necessitating an integrated, multi-faceted therapeutic approach.

In this section, the pathogenetic pathways activated by moderate exercise are described, but the effects of these pathways have not been quantified. The next interrogation was therefore whether biomarkers could quantify the CHD effect of moderate exercise. This was accomplished by using connection graphs, which link the relative effect of a health or pathogenic factor to the individual biomarkers through the pathways that are shown in Fig. 1.

Biomarkers of coronary heart disease

The integrated model that was developed is a high-level conceptual model, from which the interconnectedness of CHD is immediately apparent (Fig. 1). The model is however complicated. Biomarkers can be used as indicators of an underlying disorder and the measurement of specific biomarkers enables prediction of the RR for CHD associated with the biomarker.²⁹⁻³¹ The relevant biomarkers and their association with CHD risk per one standard deviation increase in said biomarker are given in Table 2. This can allow for the quantification of the effects of moderate exercise on the pathogenesis of CHD.

To simplify the integrated model, serological biomarkers (which can easily be measured) are used to link the effect of exercise to the corresponding RR of CHD. Fig. 2 presents a comparison of the RR associated with an array of serological biomarkers per one standard deviation increase in the biomarker.⁷

Effects of moderate exercise

Using the integrated model in Fig. 1, it is possible to account for the impact that moderate exercise would have on the serological biomarkers of CHD. This enables a simplification of the integrated model into a connection graph, which shows all the connections between moderate exercise and the measurable serological biomarkers.

The connection graph presented in Fig. 3 does not neglect any of the underlying complexity of CHD. To more clearly determine the effect of exercise on different biomarkers in Fig. 3, the biomarkers previously shown in Fig. 2 were divided into eight classes, namely vascular function and neurohormonal activity, renal function, necrosis, coagulation, oxidative stress, lipids, and metabolic and inflammatory markers.

The pathogenetic pathways (from Fig. 1) are superimposed on the connecting lines in Fig. 3. Increasing line thickness indicates a connection with possible greater pathogenetic effect (as quantified by biomarker relative-risk prediction of CHD). For example, the risk of CHD is relatively low when considering leptin, therefore the connection line between exercise and leptin is thinner than for others (e.g. Apo B).

It is intriguing to see that moderate exercise has a connection to all the serological biomarkers. This further highlights the inverse correlation between CHD risk and moderate exercise. From the connection graph in Fig. 3, it can be noted that the potential risk reduction effect of moderate exercise may be greatly influenced by changes in inflammatory, metabolic and lipid markers, which provide a considerable increased risk for CHD.²⁴

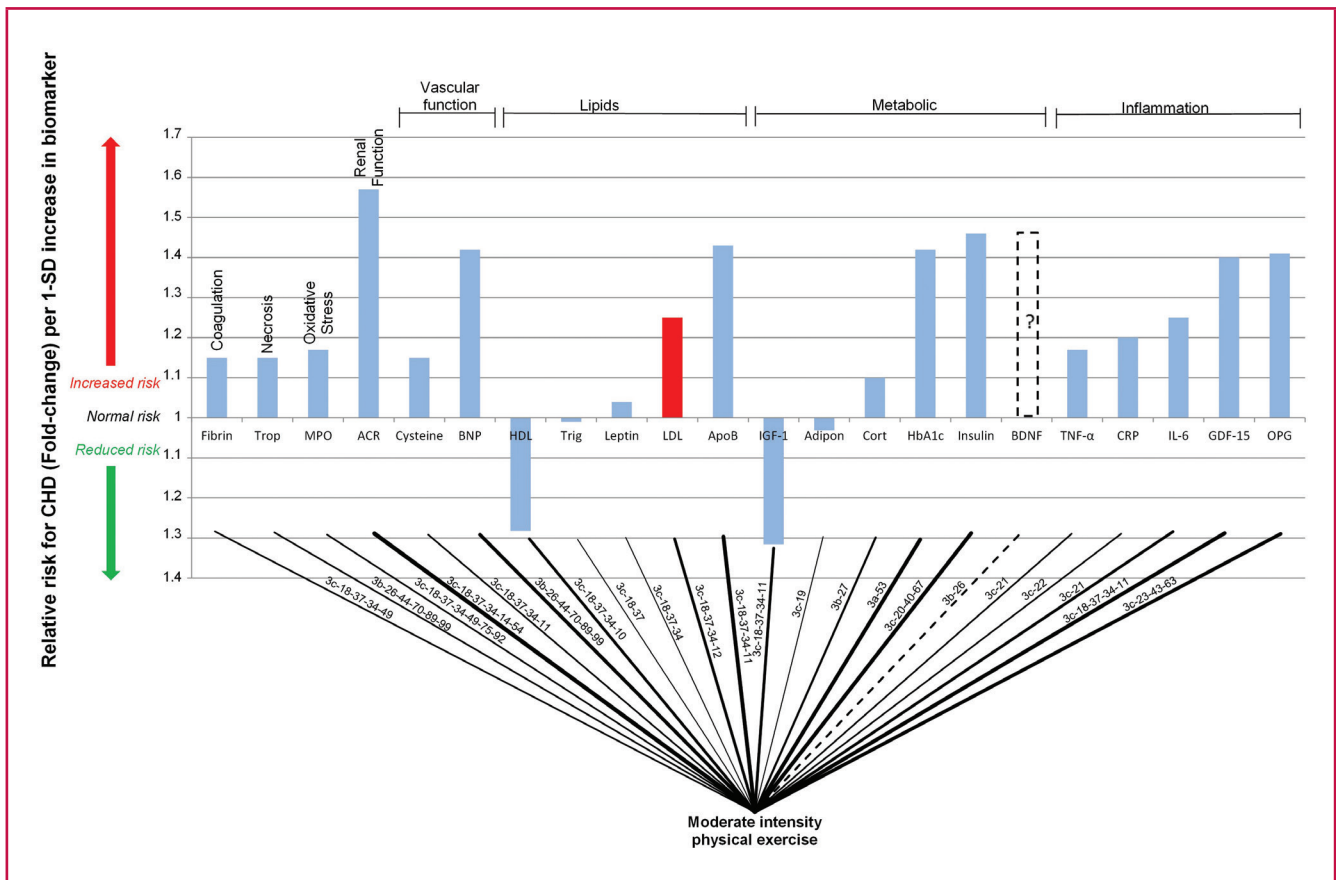


Fig. 3. Interconnection of relative risk effects of moderate exercise and serological biomarkers for CHD. ACR, albumin-to-creatinine ratio; Adipo, adiponectin; Apo B, apolipoprotein-B; BDNF, brain-derived neurotrophic factor; BNP, B-type natriuretic peptide; Cort, cortisol; CRP, C-reactive protein; cysteine, homocysteine; fibrin, fibrinogen; GDF-15, growth-differentiation factor-15; HbA_{1c}, glycosylated haemoglobin A_{1c}; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LDL, low-density lipoprotein; MPO, myeloperoxidase; OPG, osteoprotegerin; TNF- α , tumour necrosis factor- α ; Trig, triglycerides; Trop, troponins.

Mora and co-workers determined the mechanisms of the reduced risk of CHD associated with exercise in women.² They found that a reduction in inflammatory biomarkers were the largest contributors to lowered risk. These were followed, in order, by blood pressure, lipid levels, body mass index (BMI) and haemoglobin level. In the study, the combination of different individual risk factors quantified only 35.5% of the total risk reduction due to physical exercise on CHD.²

It is therefore clear that the risk factors used by Mora and co-workers, in terms of serological biomarkers, did not fully quantify the risks associated with CHD. In their study, LDL, HDL and Apo B serum levels were recorded to monitor lipid levels, but only hsCRP serum levels were used for deducing inflammatory levels.² It may therefore be possible that with the addition of the other biomarkers indicated in Fig. 3, the effect of moderate exercise may be better quantified.

In Fig. 3, it is clear from the risk associated with inflammation that reduction in inflammation would prove beneficial to CHD risk. The full extent of the relationship between exercise and inflammation has not been determined but it has been proven that chronic moderate exercise has a systemic anti-inflammatory effect.^{5,16,32} It has further been shown that the anti-inflammatory effect of exercise provides the largest individual risk-reduction component of moderate exercise in women.²

Naturally there is a strong link to the metabolic process that is manifested in the connection to the metabolic biomarkers, specifically insulin resistance and glycated haemoglobin level.^{33,34} This connection may be largely mediated by the increased expenditure of energy, which produces favourable effects on CHD pathogenesis.^{10, 23} Moderate exercise is also related to changes in lipid factors such as increases in HDL cholesterol and decreases in LDL cholesterol and Apo B levels.^{33,34}

Discussion

It is clear that there are a wide variety of effects of exercise on the pathogenesis of CHD, which can be described by the changes in biomarkers. However, from the connection graph in Fig. 3, it is not immediately clear what the overall effect of moderate exercise is on CHD. This effect has been quantified in the RR reduction for CHD, which is observed in those who engage in moderate exercise.

Moderate-intensity physical exercise of 1 100 kcal/week is associated with an average RR of 0.75 (0.71–0.79), based on a large meta-analysis.³⁵ The RR of 0.75 would correlate to a RR reduction of 1.33-fold using the method previously described in the Methods section.

The data from Fig. 3 show that inflammation and metabolic

dysregulation may be key aspects in the pathogenesis of CHD.^{5,10,16,23,32-34} These aspects decrease during exercise and may therefore play a part in the 1.33-fold decreased risk for CHD.

Based on the evidence, it is believed that the CHD benefit associated with exercise is substantial and should garner a similar level of public interest as do other risk factors such as smoking, high cholesterol levels and treatments such as statin therapy. However, while exercise is frequently advised for healthy living,³⁶ it is unfortunate that only 48.9% of Americans meet the physical activity guidelines. It follows from this that 51.1% of Americans do not meet the minimum physical activity guidelines, which results in 162.8 million Americans at a greater risk of CHD due to physical inactivity.³⁷

The individual studies selected unfortunately represent only the risk associated with the cohort studied and cannot accurately be extrapolated to other populations without further research.

Conclusion

Although it is well known that moderate exercise is associated with a lower risk of CHD, all the positive effects on CHD pathogenesis were not available in a detailed integrated model. Such a model would help provide further insight. A high-level conceptual model was therefore developed, which links moderate exercise with the pathogenesis, hallmarks and biomarkers of CHD.

The novel connection graph developed from this model shows, at a glance, the positive effect of moderate exercise on certain important aspects of the pathogenesis of CHD. It helps to graphically explain why moderate exercise is associated with lower CHD risk. From this it is apparent that exercise has a wide-ranging impact on the pathogenesis of CHD, with these effects notable in changes in CHD biomarkers.

The integrated high-level CHD model and simplified connection graph provide a summary of evidence for a causal relationship between CHD risk and moderate exercise. We acknowledge the fact that the integrated view is relevant to other lifestyle issues and for full comprehension will have to be replicated in other articles describing these factors.

The angel investor was Dr Arnold van Dyk and the research was later self-funded. Prof Leon Liebenberg was involved in the initial research.

References

- Mathers CD, Boerma T, Fat DM. Global and regional causes of death. *Br Med Bull* 2009; **92**(1): 7–32.
- Mora S, Cook N, Buring JE, Ridker PM, Lee I-M. Physical activity and reduced risk of cardiovascular events potential mediating mechanisms. *Circulation* 2007; **116**(19): 2110–2118.
- Green DJ, Spence A, Halliwill JR, Cable NT, Thijssen DH. Exercise and vascular adaptation in asymptomatic humans. *Exp Physiol* 2011; **96**(2): 57–70.
- Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, *et al.* Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: A statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* 2003; **107**(24): 3109–3116.
- Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 2011; **11**(9): 607–615.
- Mathews MJ. A systems engineering approach to coronary heart disease [PhD dissertation]. Potchefstroom: North-West University, 2016.
- Mathews MJ, Liebenberg L, Mathews EH. How do high glycemic load diets influence coronary heart disease? *Nutr Metab* 2015; **12**(1): 6.
- Mathews MJ, Liebenberg L, Mathews EH. The mechanism by which moderate alcohol consumption influences coronary heart disease. *Nutr J* 2015; **14**(1): 33.
- Mathews MJ, Mathews EH, Liebenberg L. The mechanisms by which antidepressants may reduce coronary heart disease risk. *BMC Cardiovasc Disord* 2015; **15**(1): 82.
- Strasser B. Physical activity in obesity and metabolic syndrome. *Ann NY Acad Sci* 2013; **1281**(1): 141–159.
- Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *Can Med Assoc J* 2006; **174**(6): 801–809.
- Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**(12): 1595–1607.
- Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2005; **111**(11): 1448–1454.
- Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* 1993; **259**(5091): 87–91.
- Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, *et al.* Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003; **112**(12): 1821–1830.
- Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 2005; **98**(4): 1154–1162.
- Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012; **32**(9): 2045–2051.
- Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *J Am Med Assoc* 2004; **291**(14): 1730–1737.
- Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports* 2006; **16**(S1): 3–63.
- Brown NJ, Agirbasli MA, Williams GH, Litchfield WR, Vaughan DE. Effect of activation and inhibition of the renin-angiotensin system on plasma PAI-1. *Hypertension* 1998; **32**(6): 965–971.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, *et al.* Seventh report of the joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**(6): 1206–1252.
- Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, *et al.* Clinical implications of obesity with specific focus on cardiovascular disease. A statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation* 2004; **110**(18): 2952–2967.
- Rose AJ, Richter EA. Skeletal muscle glucose uptake during exercise: how is it regulated? *Physiology* 2005; **20**(4): 260–270.
- Cimenti C, Schlagenhaut A, Leschnik B, Schretter M, Tschakert G, Gröschl W, *et al.* Low endogenous thrombin potential in trained subjects. *Thromb Res* 2013; **131**(6): e281–e285.
- Rauramaa R, Salonen JT, Seppänen K, Salonen R, Venäläinen J, Ihanainen M, *et al.* Inhibition of platelet aggregability by moderate-intensity physical exercise: a randomized clinical trial in overweight men.

- Circulation* 1986; **74**(5): 939–944.
26. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, *et al.* Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000; **342**(7): 454–460.
 27. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, *et al.* Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998; **98**(24): 2709–2715.
 28. Raastad T, Bjørø T, Hallen J. Hormonal responses to high-and moderate-intensity strength exercise. *Eur J Appl Physiol* 2000; **82**(1–2): 121–128.
 29. Libby P. Inflammation in atherosclerosis *Nature* 2002; **420**: 868–874.
 30. Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem* 2008; **54**(1): 24–38.
 31. Vasan RS. Biomarkers of cardiovascular disease molecular basis and practical considerations. *Circulation* 2006; **113**(19): 2335–2362.
 32. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clin Chim Acta* 2010; **411**(11): 785–793.
 33. Jorge MLMP, de Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz ALD, *et al.* The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. *Metabolism* 2011; **60**(9): 1244–1252.
 34. Kelley GA, Kelley KS. Efficacy of aerobic exercise on coronary heart disease risk factors. *Prev Cardiol* 2008; **11**(2): 71–75.
 35. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee I-M. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011; **124**(7): 789–795.
 36. Committee PAGA. Physical activity guidelines for Americans. Washington, DC: US Department of Health and Human Services, 2008.
 37. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, *et al.* Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation* 2013; **127**(1): e6–e245.
 38. Golbidi S, Laher I. Exercise and the cardiovascular system. *Cardiol Res Pract* 2012; **2012**: e210852.
 39. Chan D, Ng LL. Biomarkers in acute myocardial infarction. *BMC Med* 2010; **8**(1): 34.
 40. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. *Endocr Rev* 2007; **28**(5): 463–491.
 41. Myers J, Kaykha A, George S, Abella J, Zaheer N, Lear S, *et al.* Fitness versus physical activity patterns in predicting mortality in men. *Am J Med* 2004; **117**(12): 912–918.
 42. Green DJ, O'Driscoll G, Joyner MJ, Cable NT. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *J Appl Physiol* 2008; **105**(2): 766–768.
 43. Jenkins NT, Martin JS, Laughlin MH, Padilla J. Exercise-induced signals for vascular endothelial adaptations: implications for cardiovascular disease. *Curr Cardiovasc Risk Rep* 2012; **6**(4): 331–346.
 44. Høstmark AT, Ekeland GS, Beckstrøm AC, Meen HD. Postprandial light physical activity blunts the blood glucose increase. *Prev Med* 2006; **42**(5): 369–371.
 45. Boulé NG, Weisnagel SJ, Lakka TA, Tremblay A, Bergman RN, Rankinen T, *et al.* Effects of exercise training on glucose homeostasis: The HERITAGE Family study. *Diabetes Care* 2005; **28**(1): 108–114.
 46. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care* 2000; **23**(12): 1830–1834.
 47. Okutsu M, Suzuki K, Ishijima T, Peake J, Higuchi M. The effects of acute exercise-induced cortisol on CCR2 expression on human monocytes. *Brain Behav Immun* 2008; **22**(7): 1066–1071.
 48. Teixeira de Lemos E, Oliveira J, Páscoa Pinheiro J, Reis F. Regular physical exercise as a strategy to improve antioxidant and anti-inflammatory status: benefits in type 2 diabetes mellitus. *Oxid Med Cell Longev* 2012; **2012**: 15.
 49. Wang JC, Bennett M. Aging and atherosclerosis mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res* 2012; **111**(2): 245–259.
 50. Epstein FH, Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; **340**(2): 115–126.
 51. von der Thüsen JH, Borensztajn KS, Moimas S, van Heiningen S, Teeling P, van Berkel TJ, *et al.* IGF-1 has plaque-stabilizing effects in atherosclerosis by altering vascular smooth muscle cell phenotype. *Am J Pathol* 2011; **178**(2): 924–934.
 52. Shai S-Y, Sukhanov S, Higashi Y, Vaughn C, Rosen CJ, Delafontaine P. Low circulating insulin-like growth factor I increases atherosclerosis in ApoE-deficient mice. *Am J Physiol Heart Circ Physiol* 2011; **300**(5): H1898.
 53. Ruidavets J, Luc G, Machez E, Genoux A, Kee F, Arveiler D, *et al.* Effects of insulin-like growth factor 1 in preventing acute coronary syndromes: The PRIME study. *Atherosclerosis* 2011; **218**(2): 464–469.
 54. Higashi Y, Sukhanov S, Anwar A, Shai S-Y, Delafontaine P. Aging, atherosclerosis, and IGF-1. *J Gerontol A Biol Sci Med Sci* 2012; **67**(6): 626–639.
 55. Van Gaal LF, Mertens IL, Christophe E. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006; **444**(7121): 875–880.
 56. Mougios V. *Exercise Biochemistry*. Champaign, IL: Human Kinetics, 2006.
 57. Yu Z, Ye X, Wang J, Qi Q, Franco OH, Rennie KL, *et al.* Associations of physical activity with inflammatory factors, adipocytokines, and metabolic syndrome in middle-aged and older chinese people. *Circulation* 2009; **119**(23): 2969–2977.
 58. Wang TJ, Wollert KC, Larson MG, Coglianese E, McCabe EL, Cheng S, *et al.* Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. *Circulation* 2012; **126**(13): 1596–1604.
 59. Autenrieth C, Schneider A, Doering A, Meisinger C, Herder C, Koenig W, *et al.* Association between different domains of physical activity and markers of inflammation. *Med Sci Sports Exerc* 2009; **41**(9): 1706–1713.
 60. Lira FS, Rosa JC, Pimentel GD, Souza HA, Caperuto EC, Carnevali LC, *et al.* Endotoxin levels correlate positively with a sedentary lifestyle and negatively with highly trained subjects. *Lipids Health Dis* 2010; **9**(1): 82.
 61. Shanely R, Nieman D, Henson D, Jin F, Knab A, Sha W. Inflammation and oxidative stress are lower in physically fit and active adults. *Scand J Med Sci Sports* 2011: 215–223.
 62. Pedersen BK. The disease of physical inactivity—and the role of myokines in muscle–fat cross talk. *J Physiol*. 2009; **587**(23): 5559–68.
 63. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, *et al.* Major lipids, apolipoproteins, and risk of vascular disease. *J Am Med Assoc* 2009; **302**(18): 1993–2000.
 64. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, *et al.* A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes* 2011; **4**(3): 337–345.
 65. Luc G, Empana J, Morange P, Juhan-Vague I, Arveiler D, Ferrieres J, *et al.* Adipocytokines and the risk of coronary heart disease in healthy middle aged men: the PRIME study. *Int J Obes* 2009; **34**(1): 118–126.
 66. Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR,

- Gao P, *et al.* C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 2012; **367**(14): 1310–1320.
67. Kaptoge S, Seshasai SRK, Gao P, Freitag DF, Butterworth AS, Borglykke A, *et al.* Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J* 2014; **35**(9): 578–589.
68. Daniels LB, Clopton P, Laughlin GA, Maisel AS, Barrett-Connor E. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the Rancho Bernardo study. *Circulation* 2011; **123**(19): 2101–2110.
69. Mogelvang R, Pedersen SH, Flyvbjerg A, Bjerre M, Iversen AZ, Galatius S, *et al.* Comparison of osteoprotegerin to traditional atherosclerotic risk factors and high-sensitivity C-reactive protein for diagnosis of atherosclerosis. *Am J Cardiol* 2012; **109**(4): 515–520.
70. Rana JS, Arsenault BJ, Després J-P, Côté M, Talmud PJ, Ninio E, *et al.* Inflammatory biomarkers, physical activity, waist circumference, and risk of future coronary heart disease in healthy men and women. *Eur Heart J* 2009; **32**(3): 336–344.
71. Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, *et al.* B-type natriuretic peptides and cardiovascular risk systematic review and meta-analysis of 40 prospective studies. *Circulation* 2009; **120**(22): 2177–2187.
72. Humphrey LL, Fu R, Rogers K, Freeman M, Helfand M. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. *Mayo Clin Proc* 2008; **83**(11): 1203–1212.
73. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *J Am Med Assoc* 2002; **288**(16): 2015–2022.
74. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *J Am Med Assoc* 2005; **293**(13): 1609–1616.
75. Pai JK, Cahill LE, Hu FB, Rexrode KM, Manson JE, Rimm EB. Hemoglobin A_{1c} is associated with increased risk of incident coronary heart disease among apparently healthy, nondiabetic men and women. *J Am Heart Assoc* 2013; **2**(2): e000077.
76. Schneider HJ, Wallaschofski H, Volzke H, Markus MR, Doerr M, Felix SB, *et al.* Incremental effects of endocrine and metabolic biomarkers and abdominal obesity on cardiovascular mortality prediction. *PLoS One* 2012; **7**(3): e33084.
77. Kanhai D, Kranendonk M, Uiterwaal C, Graaf Y, Kappelle L, Visseren F. Adiponectin and incident coronary heart disease and stroke. A systematic review and meta-analysis of prospective studies. *Obes Rev* 2013; **14**(7): 555–567.
78. Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation* 2005; **112**(3): 332–340.
79. Hamer M, Endrighi R, Venuraju SM, Lahiri A, Steptoe A. Cortisol responses to mental stress and the progression of coronary artery calcification in healthy men and women. *PLoS One*. 2012; **7**(2): e31356.
80. Noble EE, Billington CJ, Kotz CM, Wang C. The lighter side of BDNF. *Am J Physiol Regul Integr Comp Physiol* 2011; **300**(5): R1053.
81. Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. *Trends Cogn Sci* 2011; **15**(12): 576–584.
82. Calabrese F, Molteni R, Racagni G, Riva MA. Neuronal plasticity: a link between stress and mood disorders. *Psychoneuroendocrinology* 2009; **34**: S208–S216.
83. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One* 2012; **7**(12): e52036.
-