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The mechanism by which moderate alcohol consumption influences coronary heart disease

Marc J Mathews[*], Leon Liebenberg and Edward H Mathews

Abstract

Background: Moderate alcohol consumption is associated with a lower risk for coronary heart disease (CHD). A suitably integrated view of the CHD pathogenesis pathway will help to elucidate how moderate alcohol consumption could reduce CHD risk.

Methods: A comprehensive literature review was conducted focusing on the pathogenesis of CHD. Biomarker data were further systematically analysed from 294 cohort studies, comprising 1 161 560 subjects. From the above a suitably integrated CHD pathogenetic system for the purpose of this study was developed.

Results: The resulting integrated system now provides insight into the integrated higher-order interactions underlying CHD and moderate alcohol consumption. A novel 'connection graph' further simplifies these interactions by illustrating the relationship between moderate alcohol consumption and the relative risks (RR) attributed to various measureable CHD serological biomarkers. Thus, the possible reasons for the reduced RR for CHD with moderate alcohol consumption become clear at a glance.

Conclusions: An integrated high-level model of CHD, its pathogenesis, biomarkers, and moderate alcohol consumption provides a summary of the evidence that a causal relationship between CHD risk and moderate alcohol consumption may exist. It also shows the importance of each CHD pathway that moderate alcohol consumption influences.

Keywords: Coronary heart disease, Moderate alcohol consumption, Biomarkers

Background

The World Health Organisation indicates coronary heart disease (CHD) as the leading cause of death globally [1]. It is also well documented that moderate alcohol (ethanol) consumption is associated with a lower relative risk of CHD events [2-9]. However, the precise integrated mechanisms of this lower risk are not always clear at a glance.

Possible mechanisms may be due to the direct actions of alcohol on specific pathogenetic pathways of CHD which can be measured via serological biomarkers of CHD. Typically elevations of high density lipoprotein (HDL) cholesterol levels, increases in serum adiponectin levels [10], reduction in C-reactive protein (CRP) serum levels [11], reduced serum fibrinogen levels [12], and increased insulin sensitivity [13] have all been suggested as possible positive influences of moderate alcohol consumption. However, we are not sure of the relative importance of each suggestion and if these are the only influences.

Therefore, the purpose of this study is to visually integrate information on how moderate consumption of alcohol influences the pathogenesis of CHD. These influences may then provide a useful integrated summary for the plausibility of a causal relationship between moderate alcohol consumption and a reduction in CHD risk.

Methods

The integrative view of CHD is relevant to many other health issues such as diet, depression, stress, insomnia, sleep apnoea, exercise, smoking and oral health. For full comprehension of the effect of alcohol it is replicated here from [14].

Search criteria

We searched PubMed, Science Direct, Ebsco Host, and Google Scholar for publications with "coronary heart disease"or "coronary artery disease" or "cardiovascular

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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", "hypercoagulability", "hypercholesterolaemia", "hyperglycaemia", "hyperinsulinaemia", "inflammation", and "hypertension" in the title of the study.

We also searched all major relevant specialty journals in the areas of cardiology, nutrition, alcohol consumption, endocrinology, psychoneuroendocrinology, systems biology, physiology, CHD, the metabolic syndrome and diabetes, such as *Circulation; Journal of the American College of Cardiology; Arteriosclerosis, Thrombosis and Vascular Biology; The Lancet; New England Journal of Medicine; American Journal of Medicine; Nature Medicine; Diabetes Care; Journal of Clinical Endocrinology and Metabolism; American Journal of Clinical Nutrition;* and *Journal of Physiology* for similar or related articles.

Furthermore, we selected PubMed and Google Scholar for meta-analyses with keywords "coronary heart disease" or "coronary artery disease" or "cardiovascular disease" or "CHD". We also reviewed articles referenced in primary sources and their relevant citations. However, unless cited more than 50 times, we included only articles published after 1998 as these contained the most significant data.

Study selection

Only the trends from each meta-analysis that was adjusted for the most confounding variables was used and only where sufficient information was available on that trend. This was done so that the effects of most of the potential confounders could be adjusted for. This may, however, have increased the heterogeneity between studies, as not all studies adjusted for the same confounders.

CHD was classified as the incidence of atherosclerosis, coronary artery disease, or myocardial infarction. Where results were given for cardiovascular disease these were interpreted as CHD only in scenarios where the effect of stroke could be accounted for or results were presented separately. Biomarkers were only considered if they were associated with an increased or decreased risk of CHD.

The RR data for changes in biomarker levels were extracted from the relevant publications. However, it was not the intention of this study to conduct individual meta-analyses of the individual biomarkers. Thus the RR for changes in biomarkers were, where possible, extracted from the most recent meta-analysis conducted on the specific biomarker. If no meta-analysis was available, a suitable high quality study was included. In order to limit errors in comparisons between separate biomarkers only RR values given per increase of 1-standard deviation (SD) in the biomarker level were included. This standardisation of RR to RR per 1-SD prohibits the

misrepresentation of risk due to the selection of extreme exposure contrasts [15].

Data analysis

Heterogeneity between studies was inevitable due to the large quantity of meta-analyses considered. Each underlying meta-analysis reported individually on the heterogeneity in their analysis. However, these effects were not so large as to discount the effects observed.

The individual meta-analyses also had detailed accounts of differences between studies and subgroup analyses. These aspects are not further elaborated on in this study as they were used as a measure of validity in the study inclusion process. The individual studies selected unfortunately represent only the risk associated with the cohort studied and cannot be accurately extrapolated to other populations without further research.

OR and HR were converted to RR using the approach outlined by Zou [16]. It must however be noted that some of the 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, the 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, e.g., 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. Thus, in summary: a conventional RR = 3 is presented as per normal, as a 3-fold increase in risk and a conventional RR = 0.33 is presented as a 3-fold decrease in risk (1/0.33 = 3).

Results and discussion

Integrated view of coronary heart disease

An investigation of the interconnectivity of lifestyle factors (and specifically of moderate alcohol consumption), CHD pathogenesis, and pathophysiological traits attributed with the disorder was conducted. This study was based on data extracted from published metastudies, where genetic risk factors for CHD were not considered.

A suitably integrated CHD model of the pathogenesis and serological biomarkers of moderate alcohol consumption was not found in the literature. Such a model was thus developed and is presented in Figure 1, which schematically illustrates the complexity of CHD [14].

It is however important to realize that CHD involves inputs from hundreds of gene expressions and a number of tissues. Thus, when investigating CHD, analysing the individual components of the system would not be

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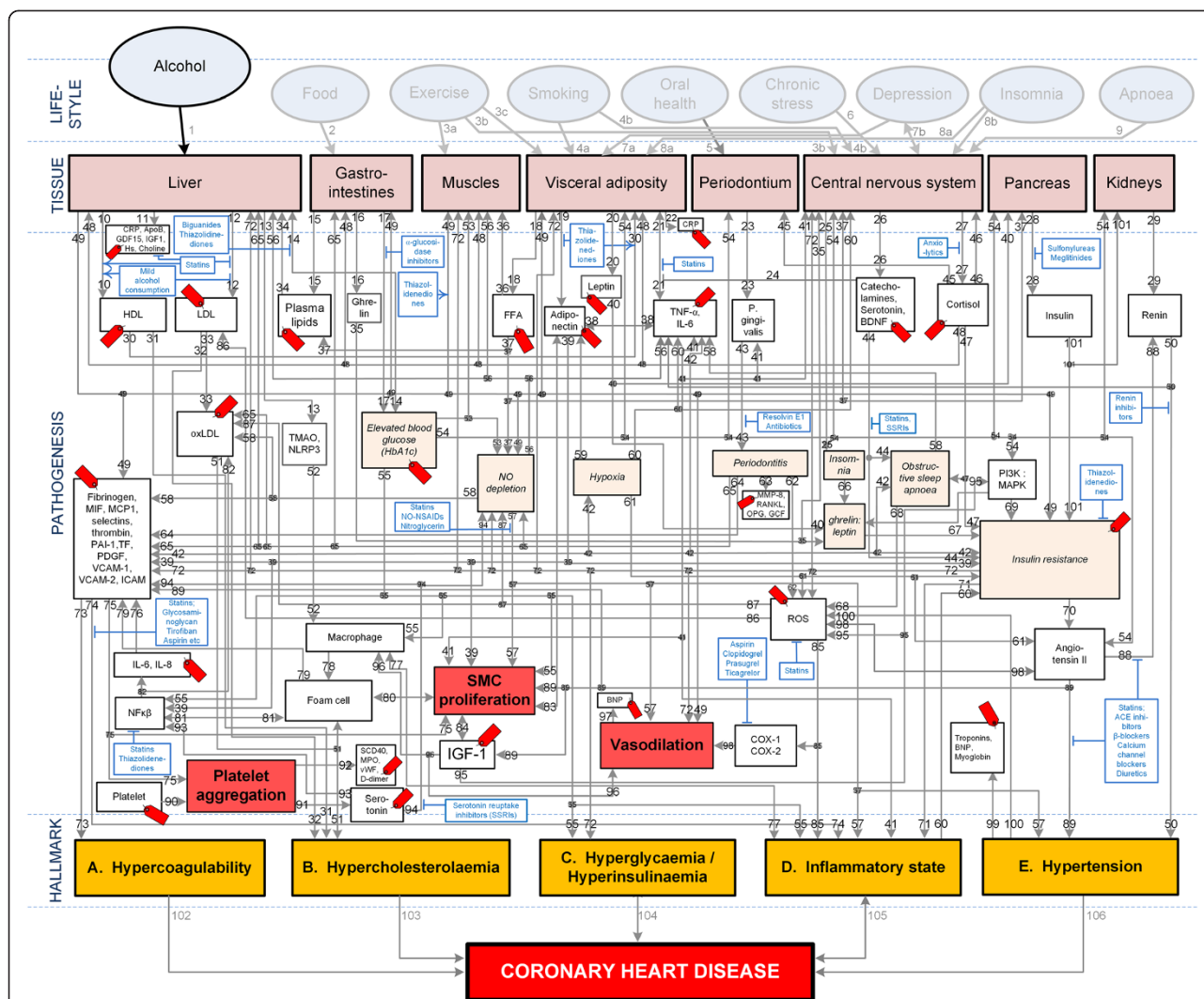
Figure 1 Conceptual model of general lifestyle factors, salient CHD pathogenetic pathways and CHD hallmarks. From "How do high glycemic load diets influence coronary heart disease?" by Mathews MJ, Liebenberg L, Mathews EH. Nutr Metab. 2015:12:6 [14]. The affective pathway of pharmacotherapeutics, blue boxes, is shown in Figure 1, and salient serological biomarkers are indicated by the ▬ icon. The blunted blue arrows denote antagonise or inhibit and pointed blue arrows denote up-regulate or facilitate. HDL denotes high-density lipoprotein; LDL, low-density lipoprotein; oxLDL, oxidised LDL; FFA, free fatty acids; TMAO, an oxidation product of trimethylamine (TMA); NLRP3, Inflammasome responsible for activation of inflammatory processes as well as epithelial cell regeneration and microflora; Hs, homocysteine; IGF-1, insulin-like growth factor-1; TNF-α, tumour necrosis factor-α; IL, interleukin; NO, nitric oxide; NO-NSAIDs, combinational NO-non-steroidal anti-inflammatory drug; SSRI, serotonin reuptake inhibitors; ROS, reactive oxygen species; NFκβ, nuclear factor-κβ; SMC, smooth muscle cell; HbA$_{1c}$, glycated haemoglobin A$_{1c}$; P. gingivalis, Porphyromonas gingivalis; vWF, von Willebrand factor; PDGF, platelet-derived growth factor; MIF, macrophage migration inhibitory factor; SCD-40, recombinant human sCD40 ligand; MPO, myeloperoxidase; MMP, matrix metalloproteinase; VCAM, vascular cell adhesion molecule; ICAM, intracellular adhesion molecule; CRP, C-reactive protein; PAI, plasminogen activator inhibitor; TF, tissue factor, MCP, monocyte chemoattractant protein; BDNF, brain-derived neurotrophic factor; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein (MAP) kinase; RANKL, receptor activator of nuclear factor kappa-beta ligand; OPG, osteoprotegerin; GCF, gingival crevicular fluid; D-dimer, fibrin degradation product D; BNP, B-type natriuretic peptide; ACE, angiotensin-converting-enzyme; COX, cyclooxygenase; β-blocker, beta-adrenergic antagonists.

sufficient, as it is also important to know how these components interact with each other [17]. For instance, genetic and lifestyle factors influence clinical traits by perturbing molecular networks [18]. A high-level systems-based view of CHD therefore has the potential to interrogate these molecular phenotypes and identify the patterns associated with the disease.

Pathways can be tracked from a chosen lifestyle factor to a hallmark of CHD if the two states are connected by the pathogenesis of the disorder. The pathways are therefore a visual representation of previously published knowledge merely integrated here. The pathogenetic pathways of interest for this review were only those between moderate alcohol consumption and CHD.

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The lifestyle factor of "Alcohol" (Figure 1) was regarded as comprising of a moderate intake of 20–30 g of alcohol (ethanol) per day for men and half that for women [9]. "Tissue" in Figure 1 indicates the organ or type of tissue which is affected by a pathogenetic pathway or trait. "Pathogenesis" in Figure 1 indicates the pathogenetic pathways of the disorder.

Salient serological biomarkers (shown in Figure 1 as ◄) and pharmacotherapeutics (shown in Figure 1 as ⊢☐) that act on the pathways are also indicated in Figure 1. These pathogenetic pathways also lead to certain traits (e.g. insulin resistance) that lead to five pathophysiological end-states, which we designate as "hallmarks of CHD", namely hypercoagulability, hypercholesterolaemia, hyperglycaemia/hyperinsulinaemia, an inflammatory state, and hypertension.

The formulation of this conceptual model required the consultation of numerous publications. The journal references which were used to describe the main pathogenetic pathways in the model are given in Table 1 [14]. It is however not the purpose of this review to describe in detail all these pathways. The aim is merely to simplify Figure 1 to elucidate only the pathways relevant to moderate alcohol consumption.

Despite the rich body of existing knowledge pertaining to CHD pathogenesis, lifestyle factors, and pharmacotherapeutics [17-21], a suitable integrated high-level conceptual model of CHD could not be found for the purpose of this study. A high-level model that consolidates the effects of moderate alcohol consumption on the RR of CHD and CHD biomarkers was thus developed. This model could thus help elucidate the higher-order interactions underlying CHD [17] and provide new insights into the relationship between CHD incidence and moderate alcohol consumption.

Pathogenetic effects of moderate alcohol consumption

Figure 1 indicates all possible pathogenetic pathways between the considered lifestyle factors and CHD. In the current review only the CHD effects of moderate alcohol consumption, detailed in Table 2, are appraised. The pathogenetic pathways which are activated by moderate alcohol consumption are elucidated therein. It is important to note that not all the pathogenetic pathways indicated in Figure 1 will be relevant in all patients, and all the pathways may not be active simultaneously.

Alcohol can serve to both reduce chronic inflammation and increase vasodilation through the regulation of insulin resistance (Figure 1, Pathways: 1-14-54-69-70-89-100-85 and 1-14-54-69-72). This is beneficial to the RR for CHD through the regulation of these hallmarks. The effect of alcohol on acute insulin sensitivity is via a direct effect on fatty acid uptake in muscle tissue [22]. Therefore, a chronic increase in insulin sensitivity is due to reductions in adipose tissue and free fatty acid availability [22].

Moderate alcohol consumption has also been found to increase serum adiponectin levels [10,23]. Increases in plasma adiponectin concentrations can further increase insulin sensitivity by increasing muscle fat oxidation [24]. (Figure 1, Pathway: 1-49-19.)

Moderate alcohol consumption acts upon the liver and can therefore serve to directly increase the hepatic production and secretion of apolipoproteins and lipoprotein particles, increase triglyceride lipase concentrations, and decrease removal of circulating high density lipoprotein cholesterol [4]. Up-regulation of HDL or inhibition of LDL results in a reduction in the incidence of hypercholesterolaemia, which is a CHD hallmark. (Figure 1, Pathways: 1-12-33-51 and 1-10-31.)

Alcohol also reduces hyperglycaemia through the inhibition of hepatic gluconeogenesis, with a resulting reduction in plasma glucose levels. Reduced plasma glucose levels serve to decrease the incidence of hyperglycaemia and hyperinsulinaemia [25], which are both CHD hallmarks. (Figure 1, Pathway: 1-14-55.) However, it is acknowledged that the over-regulation of this specific pathway could also lead to hypoglycaemia in patients with heavy alcohol use [26].

It has also been noted that moderate alcohol use reduces fibrinogen levels, clotting factors, and platelet aggregation, which affects the CHD hallmark hypercoagulability. However, the precise mechanisms governing these reductions are not known [4]. (Figure 1, Pathway 1–49 and 1-49-75.)

From the above data it may be seen that the impact of ethanol consumption on the pathogenesis of CHD may highlight the potential methods of action in the lower relative risk of CHD associated with moderate alcohol consumption. Therefore, in order to further elucidate these effects we consider the impact of alcohol consumption on the biomarkers of CHD.

Coronary heart disease biomarkers

The integrated model that was developed is a high-level conceptual model, from which the interconnectedness of CHD is immediately apparent (Figure 1). Therefore, in order to simplify the model, serological biomarkers (which quantifies the CHD pathways and which can be easily measured) were used to link the effect of moderate alcohol consumption to the corresponding risk of CHD [14].

Biomarkers can be used as indicators of an underlying disorder, such as systemic inflammation which is a known aggravating factor in the pathogenesis of CHD [27-29]. The measurement of specific biomarkers enables the prediction of the risk for CHD associated with said biomarker [30]. As it is also possible to accurately measure certain serum biomarker levels, they can be used as patient-specific links to pathogenetic or lifestyle factors (i.e. moderate alcohol consumption).

Table 1 Pathogenetic pathways (in Figure 1) and cited works

Pathway	Refs.	Pathway	Refs.	Pathway	Refs.	Pathway	Refs.	Pathway	Refs.	Pathway	Refs.
1	[4,44]	2	[45-49]	3 a,b,c	[50-52]	4 a,b	[53-55]	5	[56-58]	6	[59-61]
7 a,b	[62-67]	8 a,b	[68-70]	9	[71]	10	[30,72-75]	11	[19,30]	12	[30]
13	[47-49]	14	[19,76-83]	15	[82-84]	16	[68-70]	17	[76-83]	18	[55,85-87]
19	[84,85]	20	[68-70]	21	[19,27,28,87-91]	22	[87]	23	[92-96]	24	[97-99]
25	[68-70]	26	[97-102]	27	[34,60,61,103-114]	28	[115-119]	29	[30,120]	30	[19,30,72-75]
31	[19,30,72-75]	32	[30]	33	[30]	34	[19,84-87]	35	[68-70]	36	[19,84-87]
37	[19,84-87]	38	[28,34,121-125]	39	[84,85]	40	[68-70]	41	[27,28,125]	42	[27,119]
43	[27,28,56,92-96]	44	[97-99]	45	[59,107,109]	46	[59,107,109]	47	[59,107,109]	48	[59,107,109]
49	[115-117,126]	50	[30,122,127]	51	[17-19,21,30,120,121,127-130]	52	[47,48]	53	[19,76-83]	54	[19,76-83]
55	[19,76-83,131-136]	56	[19,84-87]	57	[19,84-87,120,137-140]	58	[19,84-87,120]	59	[110-113]	60	[110-113]
61	[110-113]	62	[56,93]	63	[92-95]	64	[56,57]	65	[56,57,94]	66	[68-70]
67	[68-70]	68	[84-87]	69	[115]	70	[115-117]	71	[30,115-117,120,141,142]	72	[30,115-117,120,141,142]
73	[19,72,119]	74	[19,72,119]	75	[72,91,119,131,138]	76	[19,27,28]	77	[27,131]	78	[27,131]
79	[19,27,72,131]	80	[19,27,72,131]	81	[27,72,131]	82	[72,115,121]	83	[133-136]	84	[27]
85	[19,121,128,139,140]	86	[19,121]	87	[121]	88	[30,121,138,141,142]	89	[30,121,138,141,142]	90	[72,131,138]
91	[97-99]	92	[30,72,129]	93	[97,98]	94	[143-146]	95	[147-150]	96	[147-150]
97	[30]	98	[27,72,121,131]	99	[30]	100	[121]	101	[115-117]	102	[30,76,79,115,121,129]
103	[19,27,30,90]	104	[19,30,121,129,138]	105	[19,27,30,90,151,152]	106	[19,30,121,129,138]				

From "How do high glycemic load diets influence coronary heart disease?" by Mathews MJ, Liebenberg L, Mathews EH. Nutr Metab. 2015:12:6 [14]. a, b, c denote the multiple pathways between lifestyle effects and CHD pathogenesis.

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Table 2 Putative effects of high-glycemic load diets and salient CHD pathogenetic pathways

Lifestyle	Pathways, and pathway numbers corresponding to those in Figure 1	Refs.
Moderate alcohol consumption	a. 1-12-↓ LDL-33-51-↓ hypercholesterolaemia	a. [3,7,8,25,26,153]
	b. 1-10-↑ HDL-31-↓ hypercholesterolaemia	b. [3,7,8,25,26,153]
	c. 1-14-↓ blood glucose-55-↓ hyperglycaemia	c. [3,7,8,25,26,153]
	d. 1-14-↓ blood glucose-54-69-↓ insulin resistance-70-89-↓ hypertension-100-↓ ROS-85-↓ inflammatory state	d. [28,153]
	e. 1-14-↓ blood glucose-54-69-↓ insulin resistance-72-↑ vasodilation	e. [128]

↑ denotes up regulation/increase, ↓ denotes down regulation/decrease, *x-y-z* indicates pathway connecting *x* to *y* to *z*. HDL, high-density lipoprotein; LDL, low-density lipoprotein; ROS, reactive oxygen species.

Table 3 Salient serological and functional biomarkers of CHD, and prospective ones

Biomarker (class and salient examples)	Prediction of CHD	Size of studies	Ref.
	Relative risk (95% CI)	(*N* = number of trials, *n* = number of patients)	
Lipid-related markers:			
HDL	0.78 (0.74-0.82)	(*N* = 68, *n* = 302 430)	[154]
Triglycerides	0.99 (0.94-1.05)	(*N* = 68, *n* = 302 430)	[154]
Leptin	1.04 (0.92-1.17)	(*n* = 1 832)	[155]
LDL	1.25 (1.18-1.33)	(*N* = 15, *n* = 233 455)	[156]
Non-HDL	1.34 (1.24-1.44)	(*N* = 15, *n* = 233 455)	[156]
ApoB	1.43 (1.35-1.51)	(*N* = 15, *n* = 233 455)	[156]
Inflammation markers:			
TNF-α	1.17 (1.09-1.25)	(*N* = 7, *n* = 6 107)	[157]
hsCRP	1.20 (1.18-1.22)	(*N* = 38, *n* = 166 596)	[158]
IL-6	1.25 (1.19-1.32)	(*N* = 25, *n* = 42 123)	[157]
GDF-15	1.40 (1.10-1.80)	(*n* = 1 740)	[159]
OPG	1.41 (1.33-1.57)	(*n* = 5 863)	[160]
Marker of oxidative stress:			
MPO	1.17 (1.06-1.30)	(*n* = 2 861)	[161]
Marker of vascular function and neurohormonal activity:			
Homocysteine	1.15 (1.09-1.22)	(*N* = 20, *n* = 22 652)	[162,163]
BNP	1.42 (1.24-1.63)	(*N* = 40, *n* = 87 474)	[164]
Coagulation marker:			
Fibrinogen	1.15 (1.13-1.17)	(*N* = 40, *n* = 185 892)	[158]
Necrosis marker:			
Troponins	1.15 (1.04-1.27)	(*n* = 3 265)	[20]
Renal function marker:			
Urinary ACR	1.57 (1.26-1.95)	(*n* = 626)	[165]
Metabolic markers:			
IGF-1	0.76 (0.56-1.04)	(*n* = 3 967)	[166]
Adiponectin	0.97 (0.86-1.09)	(*N* = 14, *n* =21 272)	[167]
Cortisol	1.10 (0.97-1.25)	(*n* = 2 512)	[168,169]
BDNF	**?**	***N/A***	[99,101,102]
HbA$_{1c}$	1.42 (1.16-1.74)	(*N* = 2, *n* = 2 442)	[170]
Insulin resistance (HOMA)	1.46 (1.26-1.69)	(*N* = 17, *n* = 51 161)	[171]

From "How do high glycemic load diets influence coronary heart disease?" by Mathews MJ, Liebenberg L, Mathews EH. Nutr Metab. 2015:12:6 [14]. *n* denotes number of participants; *N*, number of trials; ?, currently unknown RR for CHD; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin–to-creatinine ratio; GDF-15, growth-differentiation factor-15; LDL, low-density lipoprotein; HbA$_{1c}$, glycated haemoglobin A$_{1c}$; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; RANKL or OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostatic model assessment.

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A published study where all the important serum biomarkers were compared to show their relative importance regarding CHD risk prediction could not be found. This was therefore attempted in Table 3 with the corresponding results in Figure 2.

Table 3 presents the RR data from 294 cohort studies comprising 1 161 560 subjects. The results from these studies were interpreted and the averaged RR (with standard error (I) and study size (N)) was used to populate Figure 2. Figure 2 visually compares the RR of CHD associated with serological biomarkers per 1-standard deviation increase in said biomarker.

The comparative view of biomarker associated risks presented in Figure 2 elucidates the relative importance of various biomarkers of CHD. Using the array of biomarker risks and the integrated model developed in Figure 1 it is possible to display the interconnection of the pathogenesis of CHD and moderate consumption of alcohol. It may thus be possible to quantify the direct pathogenetic effects of moderate alcohol consumption on CHD through changes in biomarkers.

Effects of moderate alcohol consumption

By combining the array of biomarker risks and the pathogenetic pathways elucidated from Figure 2 a connection graph which display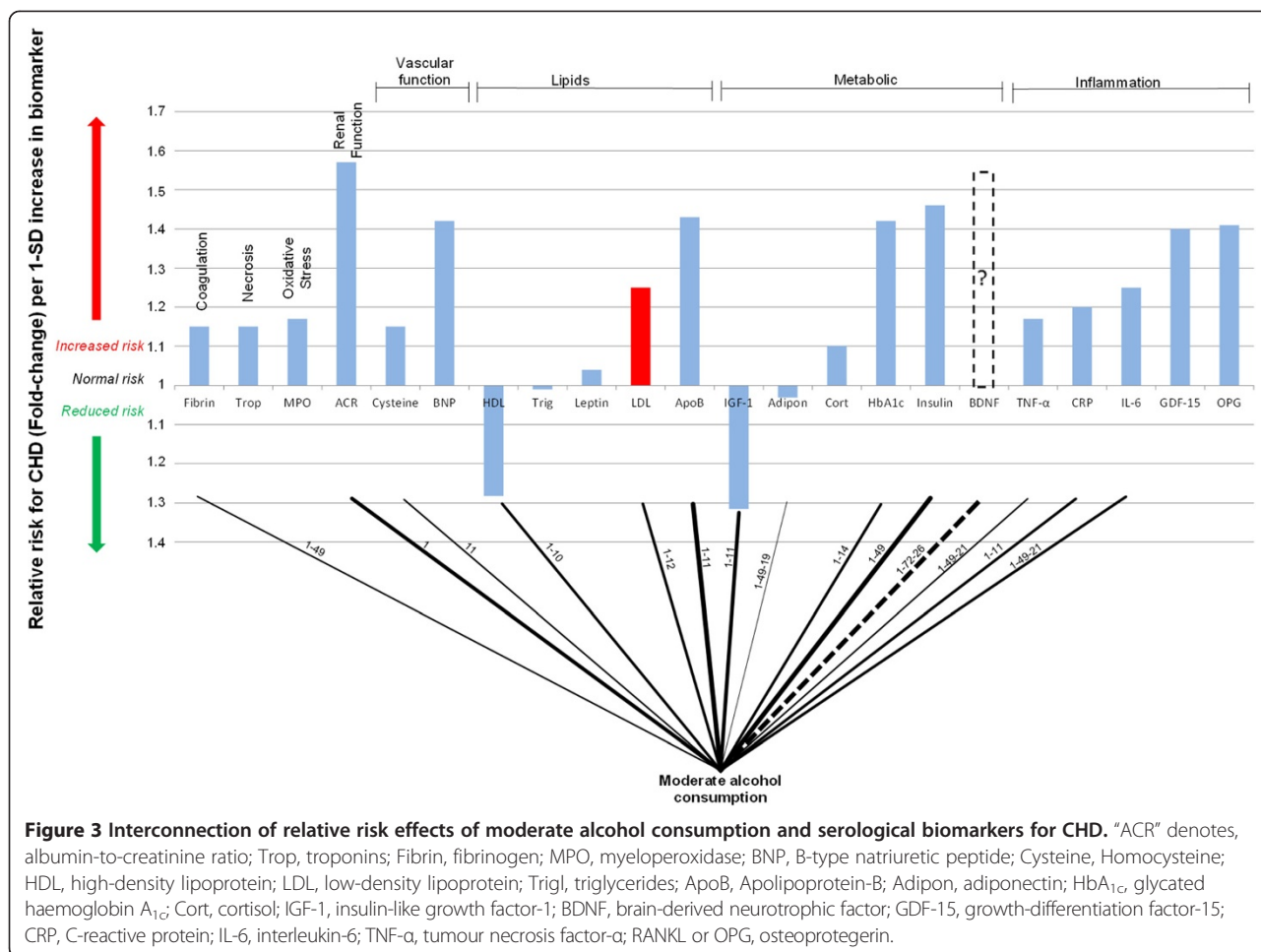s the pathogenetic connections between moderate alcohol consumption and CHD biomarker risk was developed. The pathogenetic pathways (from Figure 1), which are elucidated by the associated biomarker, are superimposed on the connecting lines in Figure 3. Increasing line thickness indicates a connection with greater pathogenetic effect (as quantified by biomarker risk prediction of CHD). For example, the risk of CHD is relatively low when considering adiponectin, thus the connection line between moderate alcohol consumption and adiponectin is thin.

From the connection graph in Figure 3 it is clear that moderate alcohol consumption is widely connected to the biomarkers associated with CHD risk. It is apparent that there are multiple connections between moderate alcohol consumption and the metabolic function biomarkers, the inflammation biomarkers, as well as a connection to the coagulation biomarker, fibrinogen.

The connections between alcohol consumption and inflammation are evident from Figure 3. The anti-inflammatory effect associated with moderate alcohol consumption could explain some of the lower CHD risk. Imhof and co-workers however found that excessive and no consumption of alcohol, led to higher serum levels of CRP compared to moderate alcohol consumption [31,32]. This indicates that excessive alcohol consumption can increase inflammation and a patient's risk for CHD, and therefore emphasises that care
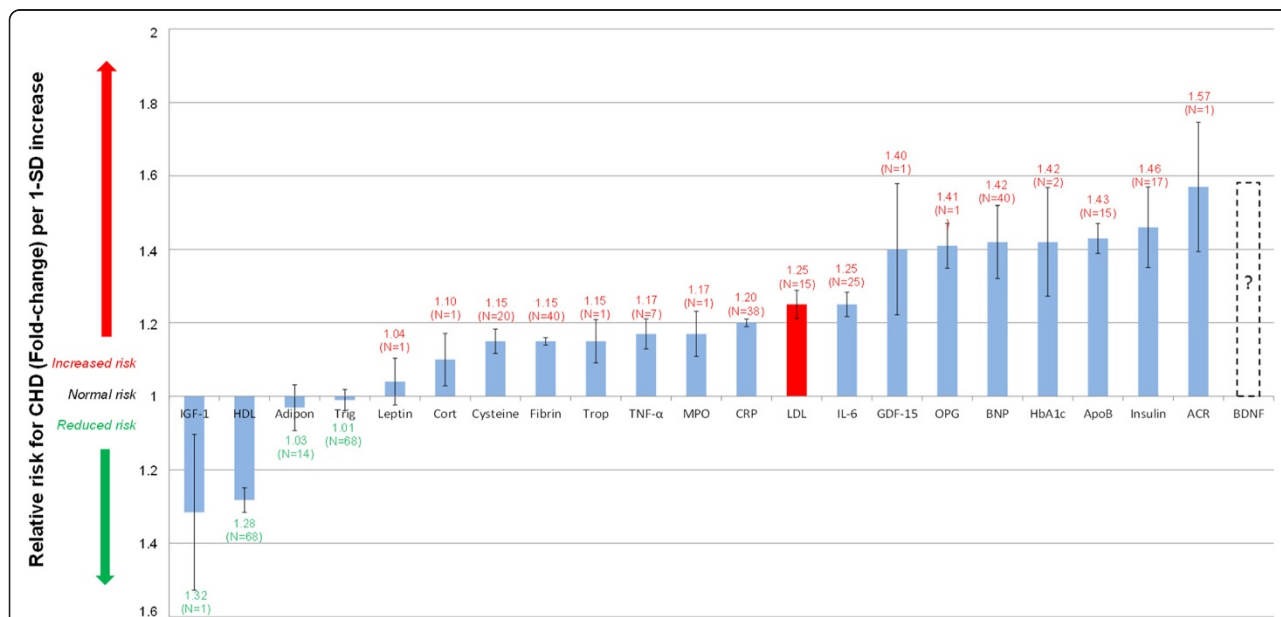
Figure 2 Normalised relative risks (fold-change) of salient current biomarkers or of potential serological biomarkers for CHD. From "How do high glycemic load diets influence coronary heart disease?" by Mathews MJ, Liebenberg L, Mathews EH. Nutr Metab.2015:12:6 [14] Increased IGF-1 and HDL levels are associated with a moderately decreased CHD risk. (IGF-1and HDL levels are significantly inversely correlated to relative risk for CHD.) N indicates number of trials; I, standard error; Adipo, adiponectin; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin-to-creatinine ratio; GDF-15, growth-differentiation factor-15; Cysteine, Homocysteine; LDL, low-density lipoprotein; HbA$_{1c}$, glycated haemoglobin A$_{1c}$; Trop, troponins; Trigl, triglycerides; CRP, C-reactive protein; IL-6, interleukin-6; Fibrin, fibrinogen; Cort, cortisol; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; RANKL or OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostasis model assessment.

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Figure 3 Interconnection of relative risk effects of moderate alcohol consumption and serological biomarkers for CHD. "ACR" denotes, albumin-to-creatinine ratio; Trop, troponins; Fibrin, fibrinogen; MPO, myeloperoxidase; BNP, B-type natriuretic peptide; Cysteine, Homocysteine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Trigl, triglycerides; ApoB, Apolipoprotein-B; Adipon, adiponectin; HbA$_{1c}$, glycated haemoglobin A$_{1c}$; Cort, cortisol; IGF-1, insulin-like growth factor-1; BDNF, brain-derived neurotrophic factor; GDF-15, growth-differentiation factor-15; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; RANKL or OPG, osteoprotegerin.

needs to be taken when contemplating moderate alcohol use as a lifestyle factor for CHD prevention [33].

Moderate alcohol intake has also been connected to an increase in adiponectin levels [10,13,23], which can lead to a reduction in adipose tissue; this in turn can increase insulin sensitivity and decrease inflammation [34]. Thus, some of the reduction in inflammation, and the concomitant decrease in CHD risk, may be accounted for by increased serum levels of adiponectin.

Various cohort studies have also observed that fibrinogen serum reduce after moderate alcohol consumption in [4,11,12,35]. This leads to a reduction in hypercoagulability, which would reduce the risk for CHD events.

Overall, the increase in HDL is thought to account for 50% of the lower CHD risk observed in those consuming alcohol in moderation [36]. The remaining lowered CHD risk is thought to be due to the anti-thrombotic effects of decreased fibrinogen serum levels [12] and increased serum levels of adiponectin [10,23].

However, from the connection graph in Figure 3 it is deemed plausible that a portion of the lower risk for CHD associated with moderate alcohol consumption

may also be due to an anti-inflammatory effect, independent of increased adiponectin levels [32].

Although the numerical values of RR presented here are based on large, clustered clinical trials, and thus give a good idea of *average* effects, it is acknowledged that individual patients will have very specific CHD profiles. However, Figure 1 is still relevant to everyone and should thus provide general insight. Therefore, Figure 1 could *inter alia* reveal pathways still available for further biomarker and drug discovery.

Discussion

It is well documented that the lowered CHD risk associated with moderate alcohol consumption is independent of beverage type [12,32,35]. This underscores the hypothesis that the lower risk of CHD associated with consuming alcohol in moderation is due to the ethanol content consumed and not the non-alcoholic components of the beverages [35].

It has however been suggested in one study that the lower risk for CHD associated with moderate alcohol consumption may be entirely due to higher socioeconomic status which is more prevalent with persons who consume

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moderate amounts of alcohol [37]. However, the results with regards to changes in serological biomarkers, as shown in Figure 3, would indicate that alcohol consumption does attributes some positive action on the pathogenesis of CHD.

The majority of studies show that moderate alcohol consumption conforms to a lower risk for CHD [4-8]. It therefore appears to validate the observation that moderate alcohol use could be a suitable lifestyle factor to consider for the prevention of CHD. However, the use of alcohol as a preventative treatment is complex due to both the potential adverse effects associated with alcohol, and as alcohol abuse contributes greatly to preventable deaths in the United States [33].

Additionally, it has been found that teetotallers and drinkers of fewer than one drink a month have a greater risk for fatal CHD than moderate and even heavy drinkers [5]. However, heavy drinkers have an increased risk of myocardial infarction [5].

Excessive alcohol consumption, more than 30 g per day, has also been associated with hypertension [38], declining ejection fraction [39], progressive left ventricular hypertrophy [40], increased risk of stroke [41], dementia [42] and overall mortality [43]. Thus, it is extremely important that alcohol use be constrained to moderate consumption levels, of 20–30 grams of ethanol per day for men and 10–15 grams of ethanol per day for women, in order to gain a potential benefit from its use.

It is further acknowledged that moderate alcohol consumption may not be possible due to religious or personal reasons. In addition, caution is advised in recommending moderate alcohol use to patients who had not previously consumed alcohol regularly, or at all [40]. Serious consideration should also be taken with patients that have a family history of alcohol abuse, addiction or depression. Furthermore, the lower risk for CHD in moderate alcohol consumers has been found to be more evident in middle-aged (50–59 years) and older adults (≥60 years) compared to younger adults (≤50 years) [3].

The current data regarding the consumption of alcohol in CHD risk reduction is based largely on observational studies [9]. However, based on the wide connection and effect of alcohol on the biomarkers, as shown in Figure 3, and pathogenetic pathways of CHD (Figures 1 and 3) it seems plausible that moderate alcohol consumption may prove a causal factor in CHD risk reduction. Thus it may be possible that the consumption of alcohol in a moderate dosage of 20–30 grams for men and 10–15 grams for women may prove beneficial to overall CHD risk.

Conclusions

Moderate alcohol consumption is associated with a lower risk of CHD. This lower risk has been observed independent of the beverage type consumed. A high-level conceptual model has been developed which links moderate alcohol consumption, and the pathogenesis and hallmarks of CHD.

This shows the positive effect of moderate alcohol consumption on certain important aspects of the pathogenesis of CHD and may explain why moderate alcohol consumption is associated with lower CHD risk. It is now clear at a glance that moderate alcohol consumption increases HDL-cholesterol, insulin sensitivity and adiponectin levels while decreasing inflammation, all of which have positive effects on the risk for CHD.

The integrated high level CHD model provides a summary of evidence for a causal relationship between CHD risk and moderate alcohol consumption.

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