Philip Morris International Research & Development

APPENDIX A6.1.4.8 HDL-C

HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

High Density Lipoprotein- Cholesterol (HDL-C)

Dr. Edward Sanders

22nd September 2015

Version: 1.0

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

TABLE OF CONTENTS

1. BACKGROUND 3
2. METHODS 4
3. FINDINGS 5
4. BIOMARKER-DISEASE LINK 7
4.1 Cardiovascular disease 7
4.2 Respiratory disease 15
4.3 Lung cancer 16
5. SMOKING-BIOMARKER LINK 17
5.1 Smoking cessation 23
5.2 Role in MRTP assessment 25
6. CONCLUSIONS 26
7. APPENDICES 28
7.1 Appendix 1 References retrieved 29
7.2 Appendix 2 Excluded studies from search 1 43
7.3 Appendix 3 Excluded studies from search 2 73
7.4 Appendix 4 Excluded studies from search 3 110

TABLE OF TABLES

Table 1. Excluded references according to exclusion criteria. 6
Table 2. Association of Smoking with HDL-C - Studies 2008-2015 18

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

1. BACKGROUND

It is well-established that smoking is causally linked to a number of diseases, particularly lung cancer, chronic obstructive pulmonary disease (COPD), and a number of forms of cardiovascular disease (CVD) [1]. It is also well-recognized that cessation of smoking reduces the risk of these diseases over time [2, 3]. For smokers who choose not to quit or who have difficulty in quitting, a possible option would be to switch to a modified risk tobacco product (MRTP). Such products may reduce the disease risks associated with smoking. This possible reduction in risk can be supported by demonstrating that one or more biological markers, or biomarkers, altered by smoking can be identified which return to normal levels in smokers who have switched to such products. A potential valid biomarker must meet three criteria: 1) it must be related to at least one health effect of smoking, 2) it must be related to smoking, and, as noted above, 3) it must return to levels equivalent to or close to those in a never smoker following smoking cessation. The goal of this report is to document that high density lipoprotein cholesterol (HDL-C) meets these three criteria and is thus a valid biomarker to establish the potential risk reduction for MRTPs.

HDL is composed of an extremely heterogeneous and variable particle population and is the densest and generally smallest of all the lipoprotein classes. HDLs are secreted from the liver or intestine as disc-shaped particles consisting primarily of phospholipids and apolipoprotein A-1 (apoA-I), although as will be seen there are many other proteins present. In the plasma, additional phospholipids, cholesterol, and other apolipoproteins are transferred to HDL causing it to increase in size with an accompanying decrease in density. HDLs have a high proportion of proteins relative to lipids with the major proteins being apoA-I and apoA-II. Among minor proteins are apoC-I, II, III, apoE, apoD and apoA-IV. Phospholipids comprise somewhat more than 50% of the HDL total lipid composition, with lesser amounts of cholesteryl esters (ca. 30%), cholesterol (ca. 10%), and triglycerides (ca. 10%). The definition of HDL-C refers only to the amount of cholesterol that is bound to HDL and provides no information as to the levels of other HDL components or as to the numbers of HDL particles. It should be noted that during the analysis of HDL-C, cholesteryl esters are hydrolyzed to cholesterol meaning that they are included in the HDL-C total [4].

HDL has been suggested to fulfill a number of biological functions. Without question, the most important of these is reverse cholesterol transfer (RCT), which will be discussed in somewhat more detail below. In brief this process involves removal of cholesterol from the plasma, macrophages, and other cells. This cholesterol is, in turn, transferred primarily to the liver and is eventually removed from the organism. The fact that cholesterol bound to HDL (HDL-C) is in the process of being removed from the organism is why HDL-C has been universally regarded as “good cholesterol.” Other functions hypothesized for HDL are: anti-oxidative activity, anti-inflammatory activity, anti-apoptotic activity, vasodilatory effects, and inhibition of platelet aggregation [5].

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

This report will document in detail the key aspects necessary to determine that HDL-C is a valid biomarker for the documentation of the short-term health effects of HDL-C. The first section will focus on published data linking HDL-C to smoking-related diseases. The vast majority of these data relate to CVD; however, there are some data relevant to lung cancer and COPD. The second section will cover studies related to the effect of smoking on HDL-C, followed by a section on smoking cessation and HDL-C. Lastly, any information on the effect of MRTPs and HDL-C levels will be discussed.

2. METHODS

Three searches of the PubMed literature data base were conducted on July 24th, 2015, for English language articles within the time frame of 2008 to the day the search was conducted.

Search 1: To identify articles primarily relevant to the association of HDL-C and smoking and/or smoking cessation using the string: (((((((HDL-C OR high density lipoprotein) AND (smokers OR smoking OR nicotine replacement OR cessation)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language].) AND Humans[Mesh])) NOT Diabetes)) NOT low density

Search 2: To identify articles primarily relevant to the association of HDL-C and CVD using the string: (((((HDL-C OR high density lipoprotein) AND (cardiovascular disease AND association) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language].)) NOT diabetes) NOT low density

Search 3: To identify articles primarily relevant to the association of HDL-C to respiratory disease using the string: ((((((HDL-C OR high density lipoprotein) AND (respiratory disease AND association) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language].) AND Humans[Mesh])) NOT Diabetes) NOT low density

The following inclusion criteria were applied:

1. Studies investigating the association of HDL-C with CVD, lung cancer, or non-malignant respiratory disease.
2. Studies investigating the association of cigarette smoking, smoking cessation, nicotine replacement therapy (NRT), or modified risk tobacco products (MRTB) on HDL-C levels.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

The following exclusion criteria were applied:

1. Association of HDL-C with factors other than smoking, MRTPs, or nicotine replacement therapy (NRT)
2. HDL-C not associated with risk of disease
3. Association of CVD with factors other than HDL-C
4. Metabolic syndrome as the endpoint or the determinant
5. Association of smoking with CVD
6. Association of HDL-C with other diseases/syndromes
7. Association of smoking with other factors or diseases/syndromes
8. Neonates, children, or adolescents
9. Environmental tobacco smoke
10. Association of COPD with other factors
11. *In vitro* or animal studies
12. Case studies

Exclusion criterion 2 is somewhat vague and includes several different categories. The most common is the use of HDL-C as a covariate used for adjustment of other associations. Also included are the use of changes in HDL-C to establish changes in hypothetical risk using risk models such as the Framingham Risk Assessment, as well as epidemiological methodological papers.

3. FINDINGS

The total of all three searches resulted in 1134 references, 453 from Search 1, 657 from Search 2, and 24 from Search 3. One hundred forty-six duplicate articles were identified leaving 988 unique references. One hundred thirty-three duplicate references were removed from Search 2, and 13 were removed from Search 3. Application of the 12 exclusion criteria listed above resulted in the exclusion of 377 articles from Search 1, 456 articles from Search 2, and 10 articles from Search 3 leaving a total of 145 retained articles. Table 1 presents the number of articles excluded from all three searches combined for each exclusion criterion.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 1. Excluded references according to exclusion criteria.

Exclusion criterion	Number of references excluded
E1 Association of HDL-C with non-relevant factors	351
E2. HDL-C not associated with disease risk	232
E3. Association of CVD with non-relevant factors	56
E4. Metabolic syndrome	86
E5. Association of smoking with CVD	25
E6. Association of HDL-C with other diseases	32
E7. Association of smoking with other factors	21
E8. Neonates, children, adolescents	22
E9. Environmental tobacco smoke	4
E10. Association of COPD with other factors	3
E11. *In vitro* or animal studies	7
E12. Case studies	4

A number of references were added. Five references were added in the BACKGROUND section, 15 references were added to the Cardiovascular disease section, six were added to the Respiratory disease section, six were added to the Lung cancer section, four were added to the SMOKING-BIOMARKER LINK section, 1 was added to the Smoking cessation section, and one was added to the Role in MRTP assessment section, giving a total of 38 additional references. Therefore, the total number of articles referenced in this report is 183.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

4. BIOMARKER-DISEASE LINK

4.1 Cardiovascular disease

It has been widely accepted for many years that there is an inverse relationship between various CVD endpoints and HDL-C levels. As noted in a recent review [6], the first publication reporting this relationship was published in 1975 by Miller et al. Since that time, numerous articles have been published the vast majority of which confirm this relationship. Perhaps most indicative of the widespread acceptance of the HDL-C/CVD association is the fact that the level of HDL-C is one of the factors to be entered into the Framingham Risk Assessment in order to predict the risk of developing coronary heart disease (CHD) within a 10-year period [7] as well as in alternative CHD risk assessment formulas.

The literature prior to 2008, the initial year of the literature searches, will not be reviewed, since, as will be seen, a large number of studies were identified by the searches. Several good reviews of the older literature were also identified [6, 8-11]. More importantly, two publications pooling multiple studies and one systematic review have been published dealing with three different CVD endpoints.

The first of these was published by the Prospective Studies Collaboration, with the most recent publication appearing in 2007 [12-14]. These investigators analyzed data from 61 prospective studies published by 1999 with data on vascular deaths (ischemic heart disease (IHD), stroke, and other causes). Although the total data set contained 892,337 apparently healthy persons resulting in 55,262 vascular deaths, data from only 153,798 persons with HDL-C information and only the 3020 IHD deaths were analyzed. There was a strong inverse relationship between HDL-C and IHD deaths irrespective of age group (40-59, 60-69, 70-79).

The second publication was by Amarenco et al. [8] who conducted a systematic review on studies investigating the association of HDL-C levels with stroke and carotid intima-media thickness (IMT). With respect to stroke, the authors analyzed ten prospective and eight case-control studies published between 1991 and 2006. The ten prospective cohort studies included 238,739 subjects amongst which 3681 incident strokes were reported. Eight of the ten cohort studies reported a statistically significant inverse relationship of HDL-C levels with incident stroke. The other two studies reported a non-significant relationship. Only three of the eight case-control studies reported a statistically significant relationship between HDL-C and stroke. A total of six prospective cohort studies and 36 cross-sectional studies were analyzed with respect to carotid IMT covering the same time period as was the case for stroke. Three of the six cohort studies reported no statistically significant relationship between HDL-C levels and carotid IMT. Two studies reported a statistically significant inverse association for combined segments, although one reported a significant result in women but not in men. The last study reported a significant result in Caucasian women but not in African American women and not in men. With respect to the cross-sectional studies, 20 showed a significant inverse association while 16 did not. The authors point out that formal meta-analyses could not be conducted on these studies because of heterogeneity in study design.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

The third review was a meta-analysis published by the Emerging Risk Factors Collaboration [15, 16]. These authors analyzed the results of 68 studies (64 prospective cohort and four nested case-control studies) that had collected baseline data on HDL-C between 1968 and 2002 representing a total of 302,430 participants. The endpoints investigated were CHD (8857 non-fatal myocardial infarctions (MI) and 3928 CHD deaths) and stroke (2534 ischemic strokes, 513 hemorrhagic strokes, and 2536 unclassified strokes). The adjusted hazard ratio (HR) for the association of HDL-C with CHD was 0.78 (95% CI, 0.74-0.82), clearly highly statistically significant. There was a much weaker association of HDL-C with stroke. The adjusted HR for ischemic stroke was 0.93 (95% CI, 0.84-1.02), 1.09 (95% CI, 0.92-1.29) for hemorrhagic stroke, and 0.87 (95% CI, 0.80-0.94) for unclassified stroke. As can be seen, only unclassified stroke was statistically significantly associated with HDL-C.

To summarize, studies published before 2008 indicate a clear, statistically inverse association of HDL-C with CHD but a much weaker relationship with both stroke and carotid IMT.

A large number of articles dealing with HDL-C levels and CVD endpoints were selected by the three literature searches. Decisions regarding exclusion of most articles using the criteria listed above could be made based on the abstract, and 147 articles were retained based on this first pass. Based on reading of the actual published paper led to the exclusion of an additional 50 studies, resulting in a total of 97 studies being retained. Given the large number of studies, the results will be only briefly summarized.

The articles were distributed into four major categories; namely, CHD, stroke, CVD events, and various endpoints. CHD (also referred to as coronary artery disease (CAD)) is defined as stable angina, unstable angina, MI and sudden coronary death [17]. There was no consistent definition for CVD events, but it frequently included CHD events, stroke, and other endpoints.

A total of seven prospective studies were identified that reported 10 estimates with respect to CHD. Five prospective studies with six estimates showed the expected statistically significant inverse relationship between HDL-C and CHD [18-22]. Two studies showed statistically significant results for females but not for males [23, 24]. One study, a retrospective cohort study, reported a positive rather than the expected negative association of HDL-C with major cardiac events including MI. However, this was a very small study in that only 10 such events were reported [25]. Eight case-control studies, for which controls were matched to cases, were identified reporting 12 estimates. All of these showed a statistically significant inverse association [26-33]. Fifteen case-control studies, where matching of controls was minimal or non-existent, with 19 estimates were retrieved. Thirteen studies with 17 estimates reported a statistically significant inverse association of HDL-C with CHD [34-46]. Two studies, however, did not report a statistically significant association. One of these studies was quite small with 42 cases and 29 controls [47]; however, the second study was of reasonable size with 241 cases and 261 controls [48]. Lastly, there were 14 cross-sectional studies with 18 estimates. Twelve studies with 15 estimates reported a statistically significant inverse association of HDL-C with CHD endpoints [49-60]. One study reported a significant

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

relationship in females but not in males [61], while one study did not report a significant association. However, this study was quite small with only 130 subjects [62]. Despite a few negative studies, these studies clearly corroborate the earlier literature with respect to there being a highly significant inverse association with HDL-C levels and CHD.

There were a rather limited number of studies that investigated the association of HDL-C with stroke. Only three prospective studies were found. The first one provided estimates for fatal and non-fatal strokes combined and for fatal strokes only. In addition, results were presented separately for males and females. A statistically significant inverse association for HDL-C was found in both males and females for combined stroke. For fatal stroke only, however, the result was significant for females but not for males [63]. The second prospective study, which provided only a single estimate, was statistically significant [64]. The third study found no statistically significant association with either ischemic or hemorrhagic stroke; however, it should be noted that this study had a large percentage of Asian subjects [18]. Two case-control studies with matched controls, each with one estimate, were found, and the inverse association for HDL-C with ischemic stroke was significant for both studies [65, 66]. Lastly, one case-control study without matched controls and one cross-sectional study were found, each reporting one estimate. Both showed a statistically significant inverse association for HDL-C with ischemic stroke [67, 68]. These results support a meaningful association of HDL-C with stroke, although there are exceptions. The older literature, as captured by the three review articles discussed above, suggest a rather weak association of HDL-C with stroke. It is difficult to compare the two sets of results given that there are several different types of stroke involved although it would appear that at least for some types of strokes, there is an association with HDL-C even though there may be a difference with respect to ethnicity.

CVD events is somewhat of a catch-all category and is not consistently defined. It will generally consist of a CHD component, frequently MI, stroke, and one other component, very often heart failure (HF). There were six prospective studies with eight estimates that determined the association of HDL-C with CVD events. Five of these studies, reporting six estimates, showed a significant inverse association [19, 69-72]. One prospective study reported a significant association with CVD events for women but not for men [73]. One randomized clinical trial was found that investigated the treatment of HIV patients with anti-retroviral treatment and compared the association of HDL-C with the presence of CVD events at baseline and reported a significant association [74]. Lastly, there were two cross-sectional studies. One of these reported a significant inverse association [75], while the other reported the anticipated association in men but not in women [76]. Therefore, there is clearly a significant inverse correlation of HDL-C with CVD endpoints. This is not surprising, given that at least one CHD endpoint is usually included in the CVD events category.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

There were a large number of various endpoints for each of which there were a limited number of studies. These will be briefly summarized.

A. Hypertension/pre-hypertension – There were four relevant studies with five estimates. One study, a case-control study without matched controls, provided two estimates, both of which showed no association of HDL-C with hypertension [77]. The remaining three studies were all cross-sectional. Two of the estimates demonstrated an inverse correlation of HDL-C with hypertension [78, 79], while the third did not [80]. Although the size of the negative cross-sectional study was quite small, the case-control studies that provided the two negative estimates were of moderate size. Therefore, an association of HDL-C with hypertension may be weak at best.
B. CVD mortality – Five studies with five estimates with CVD mortality as the end point were retrieved by the three literature searches. All of them were, not surprisingly, prospective studies. Two of these estimates showed a significant association of CVD mortality with HDL-C, whereas three did not. It would appear that there is at best a weak association of CVD mortality with HDL-C [81-85]
C. Stenosis/restenosis – Four studies providing five estimates investigated the association of HDL-C with both carotid and valvular stenosis. One prospective study reported estimates on the association of HDL-C with both mitral and aortic valve calcification, a precursor of stenosis. A statistically significant inverse relationship was reported for both [86]. Two cross-sectional studies provided data on the relationship between HDL-C and carotid stenosis/restenosis. Once again a significant inverse association was reported [87, 88]. The last study, a case-control study, found no association between HDL-C and aortic valve stenosis [89]. Despite the result, it would appear that there is indeed an association between HDL-C and stenosis.
D. Distensibility - This CVD endpoint is clearly related to stenosis. One prospective study with two estimates found a statistically significant inverse association of HDL-C with carotid artery stiffness [90] as did one cross-sectional study with two estimates [91]. However, a moderately sized cross-sectional study reported a direct correlation with aortic distensibility [92]. Despite this result, it is likely that there is a significant inverse association of HDL-C with arterial stiffness.
E. Plaque development – Development of arterial plaque is an obligatory step in the development of CAD. One prospective study with one estimate reported a statistically significant inverse association of HDL-C with the development of carotid plaque [93]. Two cross sectional studies, each with one estimate, gave similar results [94, 95]. On the other hand, a small cross-sectional study investigating the degree of arterial obstruction in CAD patients did not find a significant association [96]. Nevertheless, the evidence suggests that there is an inverse association of plaque development with HDL-C as would be expected.
F. Heart failure – There were two case-control studies, without matched controls, and one cross-sectional study, each one providing a single estimate, with HF as the endpoint. All three reported a highly statistically significant inverse association of HDL-C with this endpoint. Therefore, although based on a limited

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

number of studies, there appears to be a very clear association of reduced HDL-C levels with HF [97-99].

G. Atrial fibrillation (AF) – There were three studies providing data on AF (including data on atrial flutter and premature atrial contractions). One of these studies was based on a large randomized clinical trial evaluating the effectiveness of several medications used to treat hypertension and to reduce levels of low density lipoprotein (LDL)-cholesterol. This study provided two estimates, one at baseline and one after an average of six years of follow-up. Both estimates showed a statistically significant inverse relationship between HDL-C levels and AF/atrial flutter [100]. The other two studies were cross-sectional, and both provided a single statistically significant estimate establishing the inverse association of HDL-C levels with AF [101, 102]. Although again based on a limited number of studies, it seems clear that reduced HDL-C levels are associated with AF.

H. IMT – There were four cross sectional studies, each one providing one estimate, which reported on the association of various types of IMT with HDL-C levels. Two of these reported a statistically significant inverse association and two did not [103-106]. Therefore, there appears to be at best a weak relationship between HDL-C levels and IMT, which is consistent with the review of the older literature (Amarenco [8]).

I. Peripheral artery disease (PAD) – Two case-control studies provided one estimate each for the association of HDL-C with PAD. One of these, in which controls were matched to cases, reported a statistically significant inverse association [66]. The second study, in which controls were not matched to cases, did not find a significant association [107]. No conclusion can be drawn from these two results.

J. Miscellaneous – Seven studies located by the three searches could not be classified into any of the above groups. One of these was a prospective study providing two estimates for cardiac changes, one defined as the appearance of electrocardiogram (ECG) findings, IMT$\geq$0.8 mm, and the second as significant retinal vascular changes. A statistically significant association of these changes with HDL-C levels was reported [108]. Three studies, each with one estimate, reported significant inverse associations. The endpoint of the first study, a case-control study with matched controls, was dilated cardiomyopathy [109]. Syndrome X disease was the endpoint of the second study, a case control study with unmatched controls [110], while the hyperuraemia index was the endpoint of the third study [111]. The remaining three studies, all cross-sectional, reported no significant associations. The endpoints were left ventricular remodeling (two estimates) [112], coronary flow reserve [113], and flow-mediated dilation [114].

To summarize, the analysis of the literature from 2008 to the present clearly supports a significant association of HDL-C levels with CHD and CVD events. Association with stroke appears to be weaker, and it may well be that only certain types of stroke are associated with HDL-C levels. Although based on relatively few studies, the evidence supports a significant association of HDL-C levels with HF and AF. In addition, the evidence supports an association with hypertension, arterial stenosis, and plaque

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

development. The results for CVD mortality and for IMT are mixed, and it would appear that any association for these two endpoints with HDL-C are weak at best.

Given the well-established inverse association between HDL-C levels and a number of CVD endpoints, particularly CHD, it would be reasonable to assume that HDL-C levels would be causally associated with these CVD endpoints. Recent evidence, however, strongly indicates that this is not the case. Although there are a few papers in the past 15 years that suggest the lack of a causal relationship, the first paper that provided extremely strong evidence to this effect was published by Voight et al. in 2012 [115]. These authors identified all studies that had investigated the effect of SNPs in 15 genes known to play a role with respect to regulating HDL-C plasma levels based on genome-wide association studies. These studies were examined to determine if there was at least one gene containing a SNP that increased HDL-C levels without affecting the level of any other lipid or non-lipid cardiac risk factor. The Asn396Ser SNP in the LIPG gene, which codes for the protein endothelial lipase, was the only SNP identified, and carriers of this SNP do indeed have increased levels of HDL-C with no effect on any other cardiac risk factor. Six prospective cohort studies with a total of 50,763 participants have been conducted on the effect of the Asn396Ser SNP on cardiac risk. The pooled RR for these six studies for the association of Asn396Ser with MI was 1.10 (95% CI, 0.89-1.37, P=0.37), with no observation of heterogeneity. An additional analysis was conducted on 4 case-control studies including 16,685 cases and 48,872 controls, which provided a pooled odds ratio (OR) of 0.94 (95% CI, 0.82-1.09, P=0.41), also with no evidence of heterogeneity. The authors concluded that: "…interventions (lifestyle or pharmacological) that raise plasma HDL cholesterol cannot be assumed ipso facto to lead to a corresponding benefit with respect to risk of myocardial infarction."

The Voight et al. result implies more than simply that HDL-C is not causally related to CVD. This result also strongly supports a conclusion that despite all of the epidemiological evidence presented in this section, an increase in HDL-C does not necessarily lead to a decrease in CVD risk. In other words it does not appear to meet the requirements of a valid biomarker, and one development clearly supports this statement. Several potential drugs designed to significantly increase HDL-C levels have recently been evaluated. These drugs were designed to increase HDL-C via the inhibition of cholesteryl ester transfer protein (CETP). This protein is involved in the RCT process, briefly mentioned above, is a key contributor to the process, and plays two specific roles. The first is to transfer cholesterol, in the form of cholesteryl esters, from HDL-C to very low density lipoprotein (VLDL) particles. The VLDL-C thus formed can transfer cholesterol to the liver via the LDL receptor. Secondly, CETP is involved in the direct transfer of cholesterol from HDL-C to the liver via the scavenger receptor type B1 (SR-B1) [116]. There have been a number of molecular epidemiological studies showing that CETP is likely to play a causal role in CHD (see, for example, [117]).

The first CETP inhibitor to be evaluated was torcetrapib (CP-529,414). A phase III clinical trial of this drug was halted in 2007. Despite the fact that levels of HDL-C were increased, there was an increased risk of cardiovascular events and all-cause mortality in the treated group. Further research indicated the torcetrapib had off-target effects,

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

particularly an increase in blood pressure, which could have been responsible for these effects. The second drug of this type to be tested was dalcetrapib (JTT-705), which does not affect blood pressure. Phase III clinical testing of this drug was terminated following an interim analysis which showed that despite an increase in HDL-C in the treated group of 31-40%, compared to 4-11% in the placebo group, there was no difference in the risk of CVD events (HR = 1.04, 95% CI, 0.93-1.16). One explanation given for the failure of this drug was that inhibition of CETP would not promote and could even impair RCT. Despite the failure of these two drugs, two other similar drugs, anacetrapib (MK-0859) and evacetrapib (LY2484595) , are still in clinical trials [118].

Another issue is that recent studies have indicated that the inverse relationship of HDL-C levels with CVD events may reach a plateau at high values, or may even increase the risk of CVD events [119-121]. On the other hand, as was pointed out above, measurement of HDL-C simply determines the amount of cholesterol bound to HDL and in no way is a measure of either the actual amount of HDL present or a measure of any beneficial effects that HDL may have with respect to reducing CVD risk. That HDL, or some of its components, plays such a role is supported by studies that have found inverse associations of CVD risk with ApoA-1 levels [119, 122-124], cholesterol efflux capacity mediated by HDL (RCT) [125, 126], HDL particle number [127], and HDL anti-inflammatory properties [128].

The above discussion makes it clear that HDL-C is at best a suspect biomarker with respect to its association with CVD. This issue has not gone unnoticed by regulatory agencies. The 2011 European Society of Cardiology/European Atherosclerosis Society guidelines on the control of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) explicitly stated that “HDL-C is not recommended as a target of treatment”. Similarly, the 2013 American College of Cardiology and the American Heart Association guidelines indicate that emerging data on the use of lipid fractions other than LDL-C should not be considered as being informative [129]. Nevertheless, it is more than possible that issues with HDL-C occur only in extreme situations, and that this biomarker can be effectively used to assess short-term health effects in smokers who switch from a conventional cigarette to an MRTP. This point will be discussed in the conclusion of this report.

Although as noted above drugs designed to increase HDL-C levels via inhibition of CETP have yet to show any effectiveness with respect to reducing the risk of CVD events, there is one type of drug that clearly does reduce the risk for CHD, and at least a part of that reason may be linked to increasing levels of HDL-C or HDL constituents. These drugs are the statins. This possible effects of statins on HDL have relatively recently been reviewed by Yamashita et al. (2010) [130], and a number of the conclusions drawn in that review will be summarized.

It is well known that statins are quite effective in reducing CHD risk in many individuals who use them, and that a highly significant reason for this reduction in risk is the lowering of LDL-C levels. Statins are currently the most effective known agents for reducing LDL-C, and they are prescribed world-wide for the reduction of CHD risk. However, levels of HDL play a key role with respect to the risk of CHD as well, and

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

several statin intervention studies have shown that regression of coronary artery plaque volume is related to the HDL-C elevating effects of statins. It is important to note that different statins have differing effectiveness with respect to increasing HDL-C levels. Moreover, different results are obtained if one measures increases in HDL-C levels or in apoA-I levels. Studies have been conducted on a wide range of statins, and pitavastatin is clearly more effective in increasing HDL-C levels than five other statins that have been tested. However, simvastatin, pravastatine and rosuvastatin appear to be more effective in increasing levels of apoA-I than is pitavastatin.

As has already been discussed, RCT, the process by which cholesterol is removed from circulation and various cells such as macrophages, is one of the most important CHD protective functions of HDL. In order to understand the different roles that different statins may be playing with respect to RCT, some additional explanation of the process is necessary. Lipid-free or lipid-poor apoA-I is primarily synthesized in the liver. These particles first acquire their lipid cargo, which includes cholesterol, as they migrate out of the liver, a process that is mediated by the ATP-binding cassette transporter, ABCA1 [5, 131]. These still small, dense HDL particles are often referred to as pre-β HDL. Administration of statins have been shown to increase apoA-I levels as well as ABCA1 levels, thereby increasing the amount of pre-β HDL and the capacity of RCT.

Statins have been shown to affect two other proteins involved in RCT; namely, adiponectin and CETP. Adiponectin has been shown to promote HDL production by increasing apoA-I production in the liver as well as ABCA1 expression both in the liver and in macrophages. ABCA1 in macrophages plays a key role in transferring cholesterol to HDL and thus initiating RCT. Both pitavastatin and pravastatin have been shown to increase adiponectin levels, at least in adipocytes. Lastly, a number of statins have been shown to inhibit CETP. As discussed above, this would increase levels of HDL-C but would not be expected to either increase levels of key constituents of HDL particles, such as apoA-I or adiponectin, and would thus have no positive effect on RCT.

As noted above, HDL has been shown to exhibit anti-inflammatory properties, and this role of HDL has been suggested as contributing to its beneficial effect on CHD risk. Simvastatin treatment was shown to improve the anti-inflammatory effects of HDL using a cell-free assay. On the other hand, administration of atorvastatin to patients with rheumatoid arthritis reduced the anti-inflammatory properties of HDL. There is also evidence that statins improve the anti-oxidative properties of HDL via their effect on paraoxonase 1 (PON1). PON1 is an enzyme that hydrolyzes peroxidized lipids and is thought to have a beneficial effect on CHD risk via inhibition of oxidation of LDL and possibly of HDL itself.

As can be seen, the possible effects of statins on HDL are quite complex, and considerable research will be required to better understand these effects.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

4.2 Respiratory disease

Chronic obstructive pulmonary disease (COPD)

The association of HDL-C with various CVD endpoints has been well-known for many years, and as has been seen, numerous studies have been published. An interesting question involves a possible association of HDL-C with the other two major smoking-related diseases; namely, COPD and lung cancer. COPD will be considered in this section, while lung cancer will be covered in the next section.

Five papers of relevance to the association of HDL-C with COPD were retrieved by the literature searches. Because of the small number of papers, PubMed was searched using the term HDL cholesterol AND COPD. An additional four papers were found, and two additional papers cited as references in the nine papers already obtained were also found to be relevant. These studies fall into two main classes. The first deals with a comparison of HDL-C levels in patients compared to controls (or to patients within the same cohort without COPD), whereas the second deals with the association of HDL-C with forced expiratory volume in one second (FEV_1) in subjects without known COPD. Two case-control studies with minimal or no matching of controls, one case-cohort study, and two cross-sectional studies provided seven estimates comparing HDL-C levels in subjects with COPD to controls or subjects without COPD. The two case-control studies, the case cohort study, and one of the cross-sectional studies (five estimates) reported a statistically significant increase in HDL-C in cases compared to subjects without COPD [132-135]. The second cross-sectional study, with two estimates, reported a statistically significant increase in HDL-C in patients with restrictive airway functioning (Gold Stage I COPD) compared to controls but not in patients with obstructive airway functioning (Gold Stage II-IV COPD) [136]. This result is, of course, exactly the opposite of what has been seen for CVD. However, the situation becomes much more complicated when data on HDL-C and FEV_1 are examined. Five studies with seven estimates were found. A prospective cohort study with two estimates conducted in Japan found no significant association of HDL-C with FEV_1 values [137]. The results of three cross-sectional studies were mixed. A small study with one estimate found no association [138]. A very large cross sectional study found a statistically significant direct association of HDL-C with FEV_1; that is, lower levels of HDL-C were associated with decreased lung function [139]. The third study, of moderate size with two estimates, reported no association for males but a significant positive association in females [140]. A nested case-control study with one estimate, reported a borderline statistically significant association of HDL-C levels with FEV_1 values ($p = 0.05$) comparing subjects with FEV_1 values below normal to subjects with normal values [141]. Unlike a comparison of subjects with COPD with controls, where there is a consistent increase of HDL-C levels in subjects, there is some evidence that lower levels of HDL-C are associated with decreased lung function in apparently healthy individuals. Therefore, determining HDL-C levels in healthy individuals would perhaps be a valid biomarker for assessing lung function. However, the data are limited.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

The last study, a cross-sectional study, is technically beyond the scope of this report, since it deals with HDL levels as opposed to HDL-C levels. Interestingly HDL levels were reported to be lower in both Gold stage IV COPD patients and in patients with emphysema than in controls, which is in opposition to the results summarized above with respect to HDL-C [142]. Therefore, it is possible that HDL levels may be a more reliable marker for COPD than is HDL-C.

4.3 Lung cancer

Only two references were obtained from the three literatures searches. Therefore, PubMed was searched using the term LDH cholesterol AND lung cancer. Five additional references were found. An additional reference was identified from a citation in one of the references identified in the literature search.

All of the studies identified showed a decreased level of HDL-C in lung cancer compared to some type of control or an association of low levels of HDL-C with the risk of lung cancer. There have been two recent prospective cohort studies. The first study published by Kucharska-Newton et al. [143] found a statistically significant increased risk of lung cancer associated with low levels of HDL-C in former smokers but not in current smokers or never smokers. The explanation for this result is not obvious. The authors suggested that the result for former smokers could be a consequence of confounding by smoking. This seems unlikely. As will be seen, although smoking does indeed reduce HDL-C levels, the recovery to at least normal HDL-C levels occurs quite rapidly. The second reason will be discussed below. As far as no effect being found in current smokers, the authors hypothesized that current smoking may be such a significant risk factor that no effect of low HDL-C levels can be seen. The second prospective study [144] also found an association of low HDL-C levels with lung cancer, although they characterize this association as weak. These authors investigated a number of other cancers as well, and found a weak association of low HDL-C levels with prostate, liver and hematopoietic system cancers. Given that smoking does not appear to be a risk factor for prostate cancer, the suggestion by Kucharska-Newton et al. that confounding by smoking might explain the association of low HDL-C levels with lung cancer in ex-smokers appears to be tenuous at best.

Five relevant case-control studies, where controls were unmatched, have been published. All of them found statistically significant reduced HDL-C levels in lung cancer patients with various histological types compared to healthy controls [145-149]. It is interesting to note that Fiorenza et al. [147] reported results for five other cancers as well. HDL-C levels were reduced compared to controls in hematopoietic system, digestive system, colon, and genitourinary system cancers, but not in breast cancer.

The last study investigated levels of HDL, as opposed to HDL-C, in lung cancer patients compared to controls [150]. As was the case with COPD, HDL was also reduced in lung cancer patients.

Although there is a consistent decrease in levels of HDL-C in lung cancer patients compared to controls, the data provided by the two prospective studies is rather weak. Moreover, there is a lack of understanding as to what role HDL-C, or HDL itself, might

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

be playing. Ahn et al. [144] hypothesize that the association they report can best be explained by reverse causation. This explanation is consistent with the discussion by Chi et al. [149] suggesting that the pro-inflammatory environment known to be present in lung cancer could well explain the difference between HDL-C levels in cancer patients and controls. As a consequence, it would appear unlikely that HDL-C would be a useful biomarker for determining short-term health effects related to lung cancer.

5. SMOKING-BIOMARKER LINK

The second requirement for the qualification of HDL-C as a valid biomarker to assess short-term health effects of smoking is that smoking causes a significant and consistent decline in HDL-C levels. A meta-analysis comparing HDL-C levels in smoking to non-smoking adults was published in 1989 [151]. The pooled result for HDL-C based on 22 estimates published between 1959 and 1987 was a 5-7% decrease for smokers compared to non-smokers $p<0.001$). Sixteen studies provided data on smoking intensity that allowed a dose-response relationship to be explored. The decline in HDL-C was 8.9% in heavy smokers (>25 cig/day), 6.3% in moderate smokers (15-24 cig/day), and 4.6% in light smokers (1-14 cig/day). The p for trend was <0.001. Only one of these 22 estimates reported an increase in HDL-C levels in smokers compared to non-smokers, and that increase was 0.1%. A review published in 2008 cites three estimates, all of which confirm a decline of HDL-C in smokers compared to non-smokers [152].

A total of 18 studies investigating the effect of smoking on HDL-C levels were retrieved by the three literature searches. One additional article was found by the literature search conducted for COPD resulting in a total of 19 publications. These studies are summarized in Table 2.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2. Association of Smoking with HDL-C - Studies 2008-2015

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Result – Units mg/dL unless noted ±SD unless noted	Covariates Adjusted for [a]
1. Lavie [153]	2008, Israel	Case-control	70 (35 sm, 35 non-sm)	Cases, 46.9±9.5; controls, 45.9±11.0	91.4	Decreased in smokers (34.2±8.6) compared to non-smokers (42.6±11.3) (P = 0.0009)	b
2. Jia [154]	2009, China	Prospective cohort, median 2.86 yr follow-up	1096 (527 sm, 569 non-sm)	Sm, 53-69, non-sm 56-71	96.4 sm, 54.8 non-sm	Decreased in smokers (36.7, 31.7-43.3) compared to non-smokers (39.4 (34.0-46.0) [c] (P<0.001)	None
3. Lee [155]	2009, Taiwan	Longitudinal repeated-measures [d]	330 (2.1% female sm, 8.9% male sm)	Males, 54.9 at baseline; females, 51.9 at baseline	78.2	Decreased in male smokers by 3.6±0.9 (p = 0.0001) and by 8.4±4.9 (P = 0.09) in female smokers	Time period effect, BMI, WBC
4. De Pergola [156]	2010, Italy	Cross-sectional	931 (186 sm, 745 never-sm)	37.6±11.6	28.8	Decreased in smokers (44±1) compared to never smokers (48±1) (P<0.001)	None
5. Palacios [157]	2010, Spain	Cross-sectional	1072 (683 sm, 389 non-sm)	44.3 (38.6-48.6) [e]	77.6	OR for the reduction of HDL-C in smokers = 1.4 (95% CI, 1.0-1.8) (P = 0.04)	None

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2. Association of Smoking with HDL-C - Studies 2008-2015

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Result – Units mg/dL unless noted ±SD unless noted	Covariates Adjusted for [a]
6. Warner [158]	2010, USA	Cross-sectional	4662 (3585 sm, 1077 non-sm)	42.1±13.2 [f]	42.1 [f]	Slope of the regression line for HDL-C levels and cotinine levels = -0.0291±0.0036 (SE) (P<0.001)	Age, sex, weight, TG, alc
7. Costa Silva Zemdegs [159]	2011, Brazil	Cross-sectional	56 (smoking data not provided)	20.4±2.3	20	No statistically significant difference between HDL-C levels in smokers and non-smokers for both sexes	None
8. Ghosh [160]	2011, India	Case-control	23 (19 sm, 4 non-sm)	NS	NS	Decreased in smokers (34.4±6.8) compared to non-smokers (47.2±6.9) (P = 0.003)	None
9. Zatu [161]	2011. South Africa	Cross-sectional	258 Afr (161 sm, 97 non-sm); 372 Cauc (54 sm, 318 non-sm)	Afr, 41.6± 0.8 (SE); Cauc, 40.4±0.7 (SE)	Afr, 49.2; Cauc, 43.3	Increased in Afr smokers (63.4±1.9 (SE)) compared to non-smokers (55.7±2.7 (SE)) (p<0,001); decreased in Cauc smokers (49.9±1.9 (SE)) compared to non-smokers (54.5±0.8 (SE)) (P<0.001)	Age, sex, BMI, and WC

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2. Association of Smoking with HDL-C - Studies 2008-2015

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Result – Units mg/dL unless noted ±SD unless noted	Covariates Adjusted for [a]
10. Guven [162]	2012, Turkey	Cross-sectional	143 (50 sm, 45 non-sm)	39.2±10.5	55.8	Decreased in smokers (38±6) compared to non-smokers (45±7) (p<0.001)	None
11. Kralova Lesna [163]	2012, Czech Republic	Cross-sectional	39 (18 sm. 21 non-sm)	Sm, 50.5± 3,2; non-sm, 51.8± 2.5	0	Decreased in smokers (59.2±12.8) compared to non-smokers (76.2± 13.9) (P<0.01)	None
12. Baik [164]	2013, Korea	Prospective cohort, median follow-up 5.9 yr [g]	5314 (1262 sm, 4052 non-sm)	51.8±8.6	48.1	Decreased levels in smokers >10 cpd compared to never smokers (P<0.001)	Age, BMI, alc, phys, energy, carbo-hydrate, protein, sat fat, unsat fat, HDL-C at baseline
13. Nakamura [165]	2013, Japan	Cross-sectional	3050 (551 sm, 2499 non-sm)	55.9	50.3	Statistically significant association of decreasing levels of HDL-C in smokers in males (p for trend<0.001) but not in females (Pfor trend = 0.50)	None

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2. Association of Smoking with HDL-C - Studies 2008-2015

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Result – Units mg/dL unless noted ±SD unless noted	Covariates Adjusted for [a]
14. Overland [166]	2013, Norway	Cross-sectional	25,163 (6052 sm, 18,041 non-sm) [h]	48.6±14.3	45.1	Statistically significant decrease in HDL-C levels comparing smokers to non-smokers based on linear regression (no P value given)	Age, sex, education, phys, alc
15. Qin [167]	2013, China	Cross-sectional	1436 (770 sm, 666 non-sm)	35.0±11.3	100	No difference reported in HDL-C levels between smokers and non-smokers	None
16. Shahzad [168]	2013, India	Cross-sectional [i]	198 (87 sm, 111 non-sm)	40-60	100	Decreased in smokers (median 36, IQR = 8) compared to non-smokers (median 40, IQR = 9) (P = 0.001)	None
17. Lu [169]	2014, Scotland	Cross-sectional	10,018 (2673 sm, 7345 non-sm)	≥16	46.7	HDL-C level inversely associated with cotinine level (P for trend<0.001) [j]	Age, sex, social class, BMI, phys, alc
18. Nurjono [170]	2014, Singa-pore	Cross-sectional	61 (15 sm, 46 non-sm)	36.8±7.6	60.6	Decreased in smokers (41.8±11.6) compared to non-smokers (52.6±15-1) (P = 0.015)	None

(table continues)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Table 2. Association of Smoking with HDL-C - Studies 2008-2015

Study	Year and Country	Type of Study	Study Size	Mean Age (±SD) or Age Range	% Male	Result – Units mg/dL unless noted ±SD unless noted	Covariates Adjusted for [a]
19. Fatima [171]	2014, Pakistan	Cross-sectional	300 (150 sm, 150 non.sm)	26.6±5-5	100	Decreased in smokers (33.6±12.0) compared to non-smokers (46.4±15.8) (P<0.001)	None

Abbreviations – sm – smokers, cpd – cigarettes per day, IQR – interquartile range, NS – not specified, Afr – African, Cauc - Caucasian

Notes:

a. BMI – body mass index, WBC – white blood cell count, TG – triglycerides, alc – alcohol consumption, WC – waist circumference, phys – physical activity, energy – energy intake, sat fat – saturated fat, unsat fat – unsaturated fat

b. Controls (non-smokers) matched to cases (smokers) by age, sex, BMI, sleep apnea severity, and presence of CVD

c. Data presented as median with interquartile range

d. Subjects were evaluated four times over a four-year period

e. Mean with interquartile range

f. Taken from Roethig et al., 2009 [172]

g. The factors investigated over time were HDL-C and triglyceride levels; the data presented were obtained at end of follow-up, but they have been adjusted for baseline HDL-C levels

h. Restricted to subjects with never or previous snus use

i. This study was designed as a case control with 99 IHD patients and 101 healthy controls, but both groups were combined for the HDL-C/smoking analysis

j. Data analysed by multiple linear regression; fully adjusted coefficients are: non-smokers: cotinine 0-0.6 ng/mL, reference; 0.7-2.6 ng/mL, -0.016 (95% CI, -0.037 to 0.005); 2.7-14.9 ng/mL, -0.053 (95% CI. -0.088 to -0.018; smokers: 15.0-100 ng/mL, -0.50 (95% CI, -0.105 to 0.005); 100.1-300 ng/mL, -0.117 (95% CI, -0.145 to -0.090) (P<0.001); ≥300.1 ng/mL -0.156 (95% CI, -0.178 to -0.134) (P<0.001)

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

The 19 studies listed in Table 2 provide 23 independent estimates with respect to the difference in HDL-C levels between smokers and non-smokers. Three of the studies, were longitudinal studies, which provided four estimates; two were case-control studies, which provided one estimate each; while the remaining 14 studies accounting for 17 estimates were cross-sectional studies. These studies represent a very wide assortment of geographical areas with two studies each from China and India, and one study each from Brazil, the Czech Republic, Israel, Italy, Japan, Korea, Norway, Pakistan, Scotland, Singapore, South Africa, Spain, Taiwan, Turkey, and the United States. All six estimates from the longitudinal studies and case-control studies reported a statistically significant decrease of HDL-C levels in smokers compared to non-smokers. Of the 17 estimates based on cross-sectional studies, 13 also demonstrated a statistically significant decrease in HDL-C levels in smokers compared to non-smokers. The Costa Silva Zemdegs et al. study [159] reported no difference in HDL-C levels for either male or female smokers, but the study consisted of only 11 males and 45 females. The study by Zatu et al. [161], which was conducted in South Africa, reported a significant decrease of HDL-C levels in Caucasians but a significant increased level in Africans. Given that this was the only study that reported data on native Africans, it cannot be determined whether or not there is indeed an ethnic difference or if this result was simply an exception. Lastly, the study by Nakamura et al. [165] reported a significant decrease of HDL-C in males but no significant difference in females.

Despite the four of 23 estimates that did not report a significant decline in HDL-C levels in smokers compared to non-smokers, the data represented in Table 2 coupled with the data prior to 2008 discussed above leave no doubt that HDL-C levels are clearly and significantly reduced in smokers compared to non-smokers.

5.1 Smoking cessation

A meta-analysis reporting the effects of quitting smoking on HDL-cholesterol levels, based on the pooled result of 94 estimates based on 53 independent sets of subjects, was published in 2013 [173]. The 45 studies providing these estimates were published between 1982 and 2012. It is important to note that all of these estimates were based on within-subject changes. As a consequence, studies comparing two different groups of subjects would not have been included in this meta-analysis. Given the fact that using within-subject data avoids errors introduced by confounding, this meta-analysis represents an excellent summary of the literature dealing with the effect of smoking cessation on HDL-C levels.

Both unweighted and inverse-variance weighted results were presented. Pooling all 94 estimates indicated that HDL-C levels increased by 4.1 mg/dL (95% CI, 3.3-4.9) ($p<0.001$) following smoking cessation based on an unweighted analysis, and by 2.3 mg/dL (95% CI, 1.7-2.9) ($P<0.001$) based on an inverse-variance weighted analysis. These results demonstrate that while HDL-C levels are reduced in smokers, they are increased following smoking cessation.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

Two review articles published after 2007 were retrieved by the three literature searches [174, 175]. Both of these contain relevant information regarding smoking cessation and HDL-C levels; however, neither conducted any type of pooled analyses and only a small number of articles are cited. Both, however, conclude that the published literature confirms that smoking cessation leads to increased HDL-C levels. The more recent of the reviews [175] raises an interesting question regarding the role of various nicotine replacement therapies (NRT). They cite one study in which subjects who used transdermal nicotine patches during 35 days showed no increase in HDL-C levels. However, once the use of these patches was discontinued, HDL-C levels rose to normal over the next 42 days. Results of another study that was cited did not clarify the situation. Subjects who used a higher dose nicotine patch showed an immediate increase in HDL-C levels following smoking cessation, but those who used a lowed dose patch did not. In addition, they cite evidence indicating that the use of nicotine gum does not affect increases in HDL-C following smoking cessation. They conclude that, "The potential effects of nicotine patches during smoking cessation on plasma HDL have yet to be clarified."

The three literature searches retrieved six studies that reported results on smoking cessation and HDL-C levels. Three of these [176-178] were cited in the 2013 meta-analysis [173]. The fourth study [179] presented no useful results dealing with smoking cessation; however, it will be cited below with respect to another topic. The other two studies will be briefly described.

Andersen et al. [180] conducted a cross-sectional study on 266 pregnant women, of which 84 were smokers at the beginning of their pregnancy. Forty-one of the smokers had quit by the fifth week of gestation and remained abstinent up to the 20th week, at which point HDL-C levels were ascertained. No statistically significant difference was observed among non-smokers, ex-smokers, and continuing smokers. The second relevant article was a prospective study that followed 4168 US male physicians, drawn from the Physicians' Health Study I, for approximately 14 years [181]. The primary goal of this study was to assess the effect of lifestyle changes and the use of cholesterol modifying therapy on levels of HDL-C. A comparison of the adjusted multivariate linear regression analysis β coefficient indicated no significant change in HDL-C levels for quitters compared to continuing smokers.

Although neither of these studies reported an increase in HDL levels following smoking cessation, it is important to point out that both of them were relatively small studies. The first study, in which 41 of 84 smokers quit during the 15 week follow-up period is obvious small. The second study with a cohort of 4168 subjects might not appear small; however, there were only 244 (5.9%) smokers at baseline, and only 146 of these smokers quit during the 14 years of follow-up. The fact that the 94 estimates pooled in the 2013 meta-analysis resulted in a highly statistically significant increase in HDL-C levels following smoking cessation suggests that the negative results of these two studies can be ignored.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

There are two interesting questions regarding the increase in HDL-C levels following smoking cessation that should be considered. The first is whether or not the level returns to that of a never-smoker. The 2013 meta-analysis did not address this question. Inspection of the 20 studies shown in Table 2 revealed only one study, Baik et al. [164] that compared former smokers to never smokers. This comparison showed no significant difference in HDL-C levels between the two groups ($p = 0.44$). It should also be noted that the two review articles cited above both suggest that HDL-C levels return to normal levels following smoking cessation. Therefore, the evidence, albeit somewhat inconsistent, does suggest that levels of HDL-C to revert to normal levels following smoking cessation.

The second, and far more important, question involves the time required for a significant change in HDL-C levels to occur following smoking cessation. This point was looked at in considerable detail in the 2013 meta-analysis. There was considerable scatter in the results. Several studies show a rapid increase in the first three weeks after quitting, whereas others do not. However, most studies indicate that a maximum increase in HDL-C levels occurs from about 4-8 weeks. What may appear to be counter-intuitive is that studies that investigated multiple time points appear to show a reversal in the original HDL-C increase beyond the 4-8 week time period. A very possible reason for this is that there is considerable evidence that people who quit smoking tend to gain weight, and that weight gain depresses HDL-C levels [175, 179]. This was also addressed in the 2013 meta-analysis, where it was pointed out that HDL-C increases were substantially higher in trials where subjects were required to maintain pre-quitting diet (7.4 mg/dL) compared to studies where subjects were simply encouraged to maintain their diet (2.5 mg/dL) or studies where no constraint of any type was applied (3.2 mg/dL). These results strongly suggest that changes to HDL-C levels following switching occur relatively rapidly. Moreover, in any trial comparing changes in HDL-C levels following switching from a conventional cigarette to an MRTP, it is preferable to assess these changes after about eight weeks as opposed to longer time periods.

5.2 Role in MRTP assessment

Since the goal of this analysis is to determine if HDL-C is a valid biomarker for the evaluation of MRTPs, published studies that have evaluated change in HDL-C count for smokers who switch from a conventional cigarette to an MRTP are extremely important. Only one article was retrieved by the three literature searches. All articles related to the one article found were searched, and a second relevant reference was identified. Searching PubMed with the terms “HDL cholesterol AND electronic cigarettes” and the term “electronic cigarettes” failed to locate any further relevant references.

The first relevant reference was published by Roethig et al. in 2008 [182]. This described a randomized, controlled, forced-switching, open-label, parallel design study conducted at two clinical study centers. The purpose of the trial was to compare levels of biomarkers of exposure and certain biomarkers of effect in a group of smokers switched from their own conventional cigarette (CC) brand to an electrically heated cigarette smoking system (EHCSS) to a group that continued to smoke a CC. Ninety-seven subjects were

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

randomized, 64 into the EHCSS group and 33 into the CC group. The mean age of the subjects was 41.8+9.4 and 46% were male. The duration of the trial was 52 weeks, and subjects returned to the clinic two, four, eight, 13, 17, 21, 26, 39, and 52 weeks after switching. Eighty-two subjects completed the study. At the end of the 52-week period, HDL-C had increased by 5 mg/dL in the EHCSS group compared to 2 mg/dL in the CC group (P=0.008). This change is quite comparable to the change that would have occurred if the subjects who had switched to the EHCSS had quit smoking.

The second relevant study was published by Martin Leroy et al. in 2012 [183]. This study described a randomized, open-label, controlled study with two groups, one group that smoked an updated version of the EHCSS, while the other group smoked a CC. The duration of the trial following randomization was five weeks. A total of 316 subjects were randomized, 237 to the EHCSS group and 79 to the CC group. Subjects' mean age was 43.6+8.1 and 51% were male. Two hundred and thirty-five subjects in the EHCSS group and 75 subjects in the CC group were evaluated at the end of the five week period. Levels of HDL-C increased by 5.0+8.5 mg/dL in the EHCSS group compared to baseline (P<0.001), while a non-statistically significant increase of 0.9+7.1 mg/dL from baseline was found in the CC group. The results of this study were consistent not only with the earlier study [182] but once again with the extent of HDL-C increase that would have been anticipated from smoking cessation.

6. CONCLUSIONS

As was indicated in the BACKGROUND section of this report, for HDL-C to be a valid biomarker in order to assess the short-term health effects for individuals switching from a conventional cigarette to an MRTP, it must satisfy three conditions. One condition is that a change in HDL-C must be related to CVD endpoints. This report has clearly documented that a decline in HDL-C is highly significantly associated with CHD as well as a number of other CVD endpoints. A second condition is that smoking, which is known to be associated with an increase in risk of CHD, must also be associated with a decline in HDL-C. This report has also demonstrated a highly significant association of smoking with a decline in HDL-C levels. Lastly, cessation of smoking must be associated with an increase in HDL-C levels at least close to those found in non-smokers. This condition has also been found to be satisfied. Moreover, the change takes place rapidly, between about 4-8 weeks, meaning that monitoring smokers who have switched to an MRTP can be done in a completely feasible clinical study. In addition, although there only two relevant studies, it has also been shown that smokers who switch from a conventional cigarette to at least one type of MRTP show an increase in HDL-C levels.

There is one last issue that needs to be discussed. Recent evidence indicates that HDL-C is not causally related to CHD endpoints. More importantly, a number of studies have shown that increasing HDL-C levels does not necessarily result in a reduction of CHD risk. Does this mean that HDL-C is not a useful biomarker to assess short-term health effects of switching to an MRTP? That question can be answered by examining the situations in which an increase in HDL-C does not lead to a reduction of CHD risk. One situation involves increase in HDL-C levels by drugs such as dalcetrapib that function by

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

inhibiting CETP. As noted, inhibition of CETP may interfere with RCT, thereby neutralizing any benefit that that could be imputed to increased HDL-C levels [118]. This situation is not relevant to an increase in HDL-C levels that occurs following smoking cessation or could occur by switching to an MRTP, since neither change would be expected to interfere with the functioning of CETP. The second situation involves studies that indicate that the beneficial effects of increasing HDL-C levels reach a plateau. Three studies were cited documenting this finding. The first of these, by van der Steeg et al. [119], analyzed data from both the IDEAL study and the EPIC study. Risk estimates for a major coronary event decreased as HDL-C levels increased from <40 mg/dL in the IDEAL study until levels exceeded 70 mg/dL. Inspection of Table 2 indicates that this is a very high value that would be rarely exceeded in non-smokers. Interestingly, no real plateau was found in the EPIC study data, and risk estimates decline up to levels of HDL-C of >96.7 mg/dL. The second study, by Wilkins et al. [120], analyzed data from six community studies. There was an essentially steady decline in CHD event rate as HDL-C levels increased until levels exceeded 90 mg/dL for males, while no real plateau could be observed for females. The third study, by Qi et al. [121], was an independent prospective cohort study in which 930 subjects were followed for five years with the endpoint being plaque development. This study primarily investigated the ratio of HDL-C to HDL particles in order to determine the amount of cholesterol-overloaded HDL particles. The authors reported that relationship of this ratio to plaque development was U shaped, with low levels of HDL-C leading to increased levels of plaque development as was the case for overloaded HDL particles.

The brief analysis conducted in the preceding paragraph strongly suggests that neither of these situations would apply to the increase in HDL-C resulting from smoking cessation or that might occur when a smoker of a conventional cigarette switches to an MRTP. Smoking decreases levels of HDL-C; therefore, cessation of smoking would return HDL-C to normal levels and would not be expected to result in the very high levels where there is no longer a decrease in risk associated with increased levels. In addition, smoking cessation, or switching to an MRTP, would certainly not be expected to interfere with RCT. Lastly, it is important to note that drugs that have been documented to increase HDL-C levels are few and far between, and those that have been demonstrated to be effective, such as some statins, are known to produce at least occasional side effects. Increasing HDL-C levels via smoking cessation or switching to an MRTP has been shown to reduce the risk of smoking-related disease without leading to undesirable side effects. In conclusion, this report has demonstrated that all conditions have been satisfied to qualify HDL-C as a valid biomarker for assessing short-term health effects.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7. APPENDICES

7.1 Appendix 1 References retrieved

7.2 Appendix 2 Excluded studies from search 1

7.3 Appendix 3 Excluded studies from search 2

7.4 Appendix 4 Excluded studies from search 3

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.1 Appendix 1 References retrieved

1. U.S. Department of Health and Human Services, How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
2. U.S. Department of Health and Human Services, The health benefits of smoking cessation. U.S. Department of Health and Human Services. Public Health Service. Centers for Disease Control. Center for Chronic Disease Prevention and Health Promotion. Office on Smoking and Health., 1990. DHHS Publication No. (CDC)9O-8416.
3. Jha, P., et al., 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med, 2013. 368(4): p. 341-50.
4. Warnick, G.R., M. Nauck, and N. Rifai, Evolution of methods for measurement of HDL-cholesterol: from ultracentrifugation to homogeneous assays. Clin Chem, 2001. 47(9): p. 1579-96.
5. Kontush, A. and M.J. Chapman, Antiatherogenic small, dense HDL-guardian angel of the arterial wall? Nat Clin Pract Cardiovasc Med, 2006. 3(3): p. 144-53.
6. Graham, I., et al., Dyslipidemias in the prevention of cardiovascular disease: risks and causality. Curr Cardiol Rep, 2012. 14(6): p. 709-20.
7. National Heart, L., and Blood Institute,, Estimate of 10-year risk for coronary heart disease Framingham point scores. Available from: http://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference-html/10-year-risk-framingham-table (Accessed on 04 May 2016).
8. Amarenco, P., J. Labreuche, and P.J. Touboul, High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. Atherosclerosis, 2008. 196(2): p. 489-96.
9. Kapur, N.K., D. Ashen, and R.S. Blumenthal, High density lipoprotein cholesterol: an evolving target of therapy in the management of cardiovascular disease. Vasc Health Risk Manag, 2008. 4(1): p. 39-57.
10. Slevin, M., et al., Atherothrombosis and plaque heterology: different location or a unique disease? Pathobiology, 2008. 75(4): p. 209-25.
11. van Vliet, P., et al., The influence of age on the association between cholesterol and cognitive function. Exp Gerontol, 2009. 44(1-2): p. 112-22.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

12. Prospective Studies Collaboration, Collaborative overview ('meta-analysis') of prospective observational studies of the associations of usual blood pressure and usual cholesterol levels with common causes of death: protocol for the second cycle of the Prospective Studies Collaboration. J Cardiovasc Risk, 1999. 6(5): p. 315-20.

13. Lewington, S., et al., Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet, 2002. 360(9349): p. 1903-13.

14. Prospective Studies Collaboration, et al., Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet, 2007. 370(9602): p. 1829-39.

15. Emerging Risk Factors Collaboration, et al., The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. Eur J Epidemiol, 2007. 22(12): p. 839-69.

16. Di Angelantonio, E., et al., Major lipids, apolipoproteins, and risk of vascular disease. JAMA, 2009. 302(18): p. 1993-2000.

17. Wong, N.D., Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol, 2014. 11(5): p. 276-89.

18. Nakamura, K., et al., Does cigarette smoking exacerbate the effect of total cholesterol and high-density lipoprotein cholesterol on the risk of cardiovascular diseases? Heart, 2009. 95(11): p. 909-16.

19. Menotti, A., et al., The role of HDL cholesterol in metabolic syndrome predicting cardiovascular events. The Gubbio population study. Nutr Metab Cardiovasc Dis, 2011. 21(5): p. 315-22.

20. Hardoon, S.L., et al., Rising adiposity curbing decline in the incidence of myocardial infarction: 20-year follow-up of British men and women in the Whitehall II cohort. Eur Heart J, 2012. 33(4): p. 478-85.

21. Skretteberg, P.T., et al., HDL-cholesterol and prediction of coronary heart disease: modified by physical fitness? A 28-year follow-up of apparently healthy men. Atherosclerosis, 2012. 220(1): p. 250-6.

22. Akinkuolie, A.O., et al., High-density lipoprotein particle subclass heterogeneity and incident coronary heart disease. Circ Cardiovasc Qual Outcomes, 2014. 7(1): p. 55-63.

23. Rachas, A., et al., Clinical usefulness of the metabolic syndrome for the risk of coronary heart disease does not exceed the sum of its individual components in older men and women. The Three-City (3C) Study. Heart, 2012. 98(8): p. 650-5.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

24. Puddu, P.E., et al., Typical and atypical coronary heart disease deaths and their different relationships with risk factors. The Gubbio residential cohort study. Int J Cardiol, 2014. 173(2): p. 300-4.

25. Wenger, U., et al., Pretransplant dyslipidaemia determines outcome in lung transplant recipients. Lipids Health Dis, 2013. 12: p. 53.

26. Meiner, V., et al., Cholesteryl ester transfer protein (CETP) genetic variation and early onset of non-fatal myocardial infarction. Ann Hum Genet, 2008. 72(Pt 6): p. 732-41.

27. El Harchaoui, K., et al., High-density lipoprotein particle size and concentration and coronary risk. Ann Intern Med, 2009. 150(2): p. 84-93.

28. Jensen, M.K., et al., S447X variant of the lipoprotein lipase gene, lipids, and risk of coronary heart disease in 3 prospective cohort studies. Am Heart J, 2009. 157(2): p. 384-90.

29. Pineda, J., et al., Premature coronary artery disease in young (age <45) subjects: interactions of lipid profile, thrombophilic and haemostatic markers. Int J Cardiol, 2009. 136(2): p. 222-5.

30. Assmann, G., P. Cullen, and H. Schulte, Non-LDL-related dyslipidaemia and coronary risk: a case-control study. Diab Vasc Dis Res, 2010. 7(3): p. 204-12.

31. Iqbal, M.P., et al., Association of alkaline phosphatase with acute myocardial infarction in a population with high prevalence of hypovitaminosis D. Clin Chim Acta, 2013. 425: p. 192-5.

32. Li, X.M., et al., Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. Arterioscler Thromb Vasc Biol, 2013. 33(7): p. 1696-705.

33. Reilly, D., et al., Use of systems biology approaches to analysis of genome-wide association studies of myocardial infarction and blood cholesterol in the nurses' health study and health professionals' follow-up study. PLoS One, 2013. 8(12): p. e85369.

34. Abou-Raya, S., et al., Rheumatoid arthritis, periodontal disease and coronary artery disease. Clin Rheumatol, 2008. 27(4): p. 421-7.

35. Krecki, R., et al., Novel atherogenesis markers for identification of patients with a multivessel coronary artery disease. Kardiol Pol, 2008. 66(11): p. 1173-80; discussion 1181-2.

36. Xiao, J., et al., The apolipoprotein AII rs5082 variant is associated with reduced risk of coronary artery disease in an Australian male population. Atherosclerosis, 2008. 199(2): p. 333-9.

37. Huang, X.S., et al., Association of plasma apolipoprotein AV with lipid profiles in patients with acute coronary syndrome. Atherosclerosis, 2009. 204(2): p. e99-102.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

38. Tanrikulu, S., et al., Association of cholesteryl ester transfer protein -629C > A polymorphism with high-density lipoprotein cholesterol levels in coronary artery disease patients. Cell Biochem Funct, 2009. 27(7): p. 452-7.

39. Koc, M., et al., Clinical utility of serum cystatin C in predicting coronary artery disease. Cardiol J, 2010. 17(4): p. 374-80.

40. Sattler, K.J., et al., Sphingosine 1-phosphate levels in plasma and HDL are altered in coronary artery disease. Basic Res Cardiol, 2010. 105(6): p. 821-32.

41. Tanrikulu-Kucuk, S., et al., Cholesteryl ester transfer protein Taq1B polymorphism in an angiographically assessed Turkish population: no effects on coronary artery disease risk. Genet Test Mol Biomarkers, 2010. 14(5): p. 637-42.

42. Al-Ghamdi, A., A.A. Jiman-Fatani, and H. El-Banna, Role of Chlamydia pneumoniae, helicobacter pylori and cytomegalovirus in coronary artery disease. Pak J Pharm Sci, 2011. 24(2): p. 95-101.

43. Mansur, A.P., et al., The involvement of multiple thrombogenic and atherogenic markers in premature coronary artery disease. Clinics (Sao Paulo), 2013. 68(12): p. 1502-8.

44. Manocha, A., et al., The potential of Cystatin C and small dense LDL as biomarkers of coronary artery disease risk in a young Indian population. Mol Cell Biochem, 2014. 389(1-2): p. 59-68.

45. Serikawa, T., et al., Ratio of eicosapentaenoic acid to arachidonic acid is a critical risk factor for acute coronary syndrome in middle-aged older patients as well as younger adult patients. J Cardiol, 2014. 63(1): p. 35-40.

46. Wan, K., et al., A genetic polymorphism in RBP4 is associated with coronary artery disease. Int J Mol Sci, 2014. 15(12): p. 22309-19.

47. Watanabe, J., et al., Hemoglobin and its scavenger protein haptoglobin associate with apoA-1-containing particles and influence the inflammatory properties and function of high density lipoprotein. J Biol Chem, 2009. 284(27): p. 18292-301.

48. Salimi, S., et al., Endothelial nitric oxide synthase gene Glu298Asp polymorphism in patients with coronary artery disease. Ann Saudi Med, 2010. 30(1): p. 33-7.

49. Chen, G.L., et al., High-density lipoprotein associated factors apoA-I and serum amyloid A in Chinese non-diabetic patients with coronary heart disease. Chin Med J (Engl), 2010. 123(6): p. 658-63.

50. Kincl, V., et al., Association between laboratory markers and presence of coronary artery disease. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2010. 154(3): p. 227-33.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

51. Otsuka, F., et al., Impact of statin pretreatment on the incidence of plaque rupture in ST-elevation acute myocardial infarction. Atherosclerosis, 2010. 213(2): p. 505-11.

52. Shiga, Y., et al., Significance of serum high-density lipoprotein cholesterol levels for diagnosis of coronary stenosis as determined by MDCT in patients with suspected coronary artery disease. J Atheroscler Thromb, 2010. 17(8): p. 870-8.

53. Kajikawa, Y., et al., Association of circulating levels of leptin and adiponectin with metabolic syndrome and coronary heart disease in patients with various coronary risk factors. Int Heart J, 2011. 52(1): p. 17-22.

54. Kirhmajer, M.V., et al., Correlation of femoral intima-media thickness and the severity of coronary artery disease. Angiology, 2011. 62(2): p. 134-9.

55. Xiao, Y., et al., Relationship between lipid profiles and plasma total homocysteine, cysteine and the risk of coronary artery disease in coronary angiographic subjects. Lipids Health Dis, 2011. 10: p. 137.

56. Bilhorn, K.R., et al., High-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and cardiovascular disease in United States adults. Am J Cardiol, 2012. 110(10): p. 1464-7.

57. Malek, F., et al., Correlation of lipoprotein (a) concentration with the extent of coronary artery disease in patients on lipid lowering therapy. Neuro Endocrinol Lett, 2012. 33 Suppl 2: p. 55-9.

58. Bertolini, S., et al., Spectrum of mutations and phenotypic expression in patients with autosomal dominant hypercholesterolemia identified in Italy. Atherosclerosis, 2013. 227(2): p. 342-8.

59. Vafaeimanesh, J., et al., Association of Helicobacter pylori infection with coronary artery disease: is Helicobacter pylori a risk factor? ScientificWorldJournal, 2014. 2014: p. 516354.

60. Yunke, Z., L. Guoping, and C. Zhenyue, Triglyceride-to-HDL cholesterol ratio. Predictive value for CHD severity and new-onset heart failure. Herz, 2014. 39(1): p. 105-10.

61. Zhu, C., et al., Association of serum gamma-glutamyltransferase with arterial stiffness in established coronary artery disease. Angiology, 2013. 64(1): p. 15-20.

62. Staniak, H.L., et al., Association between postprandial triglycerides and coronary artery disease detected by coronary computed tomography angiography. Atherosclerosis, 2014. 233(2): p. 381-6.

63. Asplund, K., et al., Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. Stroke, 2009. 40(7): p. 2319-26.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

64. van den Bogaard, B., et al., On-treatment lipoprotein components and risk of cerebrovascular events in the Treating to New Targets study. Eur J Clin Invest, 2011. 41(2): p. 134-42.

65. Gan, X.M., et al., Predicting the incidence risk of ischemic stroke in a hospital population of southern China: a classification tree analysis. J Neurol Sci, 2011. 306(1-2): p. 108-14.

66. Daly, C., et al., Homocysteine increases the risk associated with hyperlipidaemia. Eur J Cardiovasc Prev Rehabil, 2009. 16(2): p. 150-5.

67. Jin, X., et al., Association of sterol regulatory element-binding transcription factor gene polymorphisms with ischaemic stroke. J Int Med Res, 2012. 40(1): p. 157-66.

68. Uchida, E., et al., Monocyte chemoattractant protein-1 is associated with silent cerebral infarction in patients on haemodialysis. Intern Med J, 2012. 42(1): p. 29-34.

69. Ridker, P.M., et al., C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation, 2008. 118(22): p. 2243-51, 4p following 2251.

70. Sprengers, R.W., et al., Prediction rule for cardiovascular events and mortality in peripheral arterial disease patients: data from the prospective Second Manifestations of ARTerial disease (SMART) cohort study. J Vasc Surg, 2009. 50(6): p. 1369-76.

71. Corsetti, J.P., et al., Apolipoprotein E predicts incident cardiovascular disease risk in women but not in men with concurrently high levels of high-density lipoprotein cholesterol and C-reactive protein. Metabolism, 2012. 61(7): p. 996-1002.

72. Dhana, K., et al., Anthropometric measures in cardiovascular disease prediction: comparison of laboratory-based versus non-laboratory-based model. Heart, 2015. 101(5): p. 377-83.

73. Marino, M., et al., Quantifying cardiometabolic risk using modifiable non-self-reported risk factors. Am J Prev Med, 2014. 47(2): p. 131-40.

74. Duprez, D.A., et al., Lipoprotein particle subclasses, cardiovascular disease and HIV infection. Atherosclerosis, 2009. 207(2): p. 524-9.

75. Teh, R., et al., How is the risk of undernutrition associated with cardiovascular disease among individuals of advanced age? J Nutr Health Aging, 2010. 14(9): p. 737-43.

76. Novelletto, B.F., S. Guzzinati, and A. Avogaro, Prevalence of metabolic syndrome and its relationship with clinically prevalent cardiovascular disease in the Veneto region, northeastern Italy. Metab Syndr Relat Disord, 2012. 10(1): p. 56-62.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

77. Liang, J.Q., et al., Association of a CYP4A11 polymorphism and hypertension in the Mongolian and Han populations of China. Genet Mol Res, 2014. 13(1): p. 508-17.

78. Ray, S., B. Kulkarni, and A. Sreenivas, Prevalence of prehypertension in young military adults & its association with overweight & dyslipidaemia. Indian J Med Res, 2011. 134: p. 162-7.

79. Wakabayashi, I., Alcohol intake and triglycerides/high-density lipoprotein cholesterol ratio in men with hypertension. Am J Hypertens, 2013. 26(7): p. 888-95.

80. Sathiyapriya, V., et al., Association between protein bound sialic acid and high sensitivity C-reactive protein in prehypertension: a possible indication of underlying cardiovascular risk. Clin Exp Hypertens, 2008. 30(5): p. 367-74.

81. Batty, G.D., et al., Does IQ predict total and cardiovascular disease mortality as strongly as other risk factors? Comparison of effect estimates using the Vietnam Experience Study. Heart, 2008. 94(12): p. 1541-4.

82. Freitas, H.F., et al., Association of HDL cholesterol and triglycerides with mortality in patients with heart failure. Braz J Med Biol Res, 2009. 42(5): p. 420-5.

83. Chawla, V., et al., Hyperlipidemia and long-term outcomes in nondiabetic chronic kidney disease. Clin J Am Soc Nephrol, 2010. 5(9): p. 1582-7.

84. Rahilly-Tierney, C., et al., High-density lipoprotein and mortality before age 90 in male physicians. Circ Cardiovasc Qual Outcomes, 2012. 5(3): p. 381-6.

85. Zewinger, S., et al., HDL cholesterol is not associated with lower mortality in patients with kidney dysfunction. J Am Soc Nephrol, 2014. 25(5): p. 1073-82.

86. Thanassoulis, G., et al., Associations of long-term and early adult atherosclerosis risk factors with aortic and mitral valve calcium. J Am Coll Cardiol, 2010. 55(22): p. 2491-8.

87. Topakian, R., et al., Postprocedural high-density lipoprotein cholesterol predicts carotid stent patency at 1 year. Eur J Neurol, 2008. 15(2): p. 179-84.

88. Mitsutake, R., et al., Are metabolic factors associated with coronary artery stenosis on MDCT? Circ J, 2009. 73(1): p. 132-8.

89. Arsenault, B.J., et al., Evaluation of links between high-density lipoprotein genetics, functionality, and aortic valve stenosis risk in humans. Arterioscler Thromb Vasc Biol, 2014. 34(2): p. 457-62.

90. Caviezel, S., et al., Sex-specific associations of cardiovascular risk factors with carotid stiffness-results from the SAPALDIA cohort study. Atherosclerosis, 2014. 235(2): p. 576-84.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

91. Zhao, W., et al., Association of lipid profiles and the ratios with arterial stiffness in middle-aged and elderly Chinese. Lipids Health Dis, 2014. 13: p. 37.

92. Malayeri, A.A., et al., Relation of aortic wall thickness and distensibility to cardiovascular risk factors (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol, 2008. 102(4): p. 491-6.

93. Xie, W., et al., Five-year change in systolic blood pressure is independently associated with carotid atherosclerosis progression: a population-based cohort study. Hypertens Res, 2014. 37(10): p. 960-5.

94. da Luz, P.L., et al., High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. Clinics (Sao Paulo), 2008. 63(4): p. 427-32.

95. Mauriello, A., et al., A pathobiologic link between risk factors profile and morphological markers of carotid instability. Atherosclerosis, 2010. 208(2): p. 572-80.

96. Penalva, R.A., et al., Lipid profile and intensity of atherosclerosis disease in acute coronary syndrome. Arq Bras Cardiol, 2008. 90(1): p. 24-30.

97. Kerola, T., et al., High-density lipoprotein is superior to B-type natriuretic peptide as a marker of systolic dysfunction in an elderly general population. Scand J Clin Lab Invest, 2009. 69(8): p. 865-72.

98. Kim, J.B., et al., Heart failure is associated with impaired anti-inflammatory and antioxidant properties of high-density lipoproteins. Am J Cardiol, 2013. 112(11): p. 1770-7.

99. Asselin, C., et al., Circulating levels of linoleic acid and HDL-cholesterol are major determinants of 4-hydroxynonenal protein adducts in patients with heart failure. Redox Biol, 2014. 2: p. 148-55.

100. Haywood, L.J., et al., Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). J Am Coll Cardiol, 2009. 54(22): p. 2023-31.

101. Conen, D., et al., Premature atrial contractions in the general population: frequency and risk factors. Circulation, 2012. 126(19): p. 2302-8.

102. Wan, Y.F., et al., Uric acid levels in obstructive sleep apnea patients with atrial fibrillation. Arch Med Res, 2014. 45(2): p. 132-7.

103. Nagai, M., et al., Visit-to-visit blood pressure variations: new independent determinants for carotid artery measures in the elderly at high risk of cardiovascular disease. J Am Soc Hypertens, 2011. 5(3): p. 184-92.

104. Nakatani, K., et al., Serum apolipoprotein B-48 levels are correlated with carotid intima-media thickness in subjects with normal serum triglyceride levels. Atherosclerosis, 2011. 218(1): p. 226-32.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

105. Paradossi, U., et al., Weight is an independent predictor of vascular injury in healthy volunteers with aspartate allele. J Cardiovasc Med (Hagerstown), 2012. 13(5): p. 307-12.

106. Pirro, M., et al., On-treatment C-reactive protein and HDL cholesterol levels in patients at intermediate cardiovascular risk: impact on carotid intima-media thickness. Life Sci, 2013. 93(8): p. 338-43.

107. Zagura, M., et al., Aortic stiffness and vitamin D are independent markers of aortic calcification in patients with peripheral arterial disease and in healthy subjects. Eur J Vasc Endovasc Surg, 2011. 42(5): p. 689-95.

108. Abe, T., et al., Hypertension is a major risk factor for future atherosclerotic changes in the Japanese population. Ann Clin Biochem, 2010. 47(Pt 2): p. 118-24.

109. Skwarek, M., et al., Significance of dyslipidaemia in patients with heart failure of unexplained aetiology. Kardiol Pol, 2008. 66(5): p. 515-22, discussion 523-4.

110. Sesal, C., et al., Role of angiotensin converting enzyme, paraoxonase 1 55, 192 gene polymorphisms in syndrome X and coronary heart disease. Pak J Biol Sci, 2009. 12(1): p. 46-51.

111. Ferré, R., et al., High-density lipoprotein cholesterol and apolipoprotein A1 levels strongly influence the reactivity of small peripheral arteries. Atherosclerosis, 2011. 216(1): p. 115-9.

112. Velagaleti, R.S., et al., Cross-sectional relations of lipid concentrations to left ventricular structural attributes. Am J Cardiol, 2010. 105(9): p. 1297-9.

113. Lee, D.H., et al., Coronary flow reserve is a comprehensive indicator of cardiovascular risk factors in subjects with chest pain and normal coronary angiogram. Circ J, 2010. 74(7): p. 1405-14.

114. Makinen, J.I., et al., Endogenous testosterone and brachial artery endothelial function in middle-aged men with symptoms of late-onset hypogonadism. Aging Male, 2011. 14(4): p. 237-42.

115. Voight, B.F., et al., Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. The Lancet, 2012. 380: p. 572-580.

116. Assmann, G. and J.R. Nofer, Atheroprotective effects of high-density lipoproteins. Annual Review of Medicine, 2003. 54: p. 321-341.

117. Ridker, P.M., et al., Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: Genomewide analysis among 18 245 initially healthy women from the Women's Genome Health Study. Circ Cardiovasc Genet, 2009. 2(1): p. 26-33.

118. Larach, D.B., M. Cuchel, and D.J. Rader, Monogenic causes of elevated HDL cholesterol and implications for development of new therapeutics. Clin Lipidol, 2013. 8(6): p. 635-648.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

119. van der Steeg, W.A., et al., High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. J Am Coll Cardiol, 2008. 51(6): p. 634-42.

120. Wilkins, J.T., et al., Coronary heart disease risks associated with high levels of HDL cholesterol. J Am Heart Assoc, 2014. 3(2): p. e000519.

121. Qi, Y., et al., Cholesterol-overloaded HDL particles are independently associated with progression of carotid atherosclerosis in a cardiovascular disease-free population: a community-based cohort study. J Am Coll Cardiol, 2015. 65(4): p. 355-63.

122. Boes, E., et al., Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: a systematic in-depth review. Exp Gerontol, 2009. 44(3): p. 136-60.

123. Sung, K.C., S.H. Wild, and C.D. Byrne, Controlling for apolipoprotein A-I concentrations changes the inverse direction of the relationship between high HDL-C concentration and a measure of pre-clinical atherosclerosis. Atherosclerosis, 2013. 231(2): p. 181-6.

124. Sung, K.C., et al., An increased high-density lipoprotein cholesterol/apolipoprotein A-I ratio is associated with increased cardiovascular and all-cause mortality. Heart, 2015. 101(7): p. 553-8.

125. Khera, A.V., et al., Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med, 2011. 364(2): p. 127-35.

126. Rohatgi, A., et al., HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med, 2014. 371(25): p. 2383-93.

127. Mora, S., R.J. Glynn, and P.M. Ridker, High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation, 2013. 128(11): p. 1189-97.

128. Dullaart, R.P., et al., The HDL anti-inflammatory function is impaired in myocardial infarction and may predict new cardiac events independent of HDL cholesterol. Clin Chim Acta, 2014. 433: p. 34-8.

129. Ray, K.K., et al., The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Eur Heart J, 2014. 35(15): p. 960-8.

130. Yamashita, S., et al., Molecular mechanisms of HDL-cholesterol elevation by statins and its effects on HDL functions. J Atheroscler Thromb, 2010. 17(5): p. 436-51.

131. Rosenson, R.S., et al., Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation, 2012. 125.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

132. Tisi, G.M., et al., Increased high density lipoprotein cholesterol in obstructive pulmonary disease (predominant emphysematous type). Metabolism, 1981. 30(4): p. 340-6.

133. Reed, R.M., et al., Advanced chronic obstructive pulmonary disease is associated with high levels of high-density lipoprotein cholesterol. J Heart Lung Transplant, 2011. 30(6): p. 674-8.

134. Acay, A., et al., Evaluation of serum paraoxonase and arylesterase activities in subjects with asthma and chronic obstructive lung disease. Clin Lab, 2013. 59(11-12): p. 1331-7.

135. Burkart, K.M., et al., APOM and high-density lipoprotein cholesterol are associated with lung function and per cent emphysema. Eur Respir J, 2014. 43(4): p. 1003-17.

136. Ford, E.S., et al., Elevated cardiovascular risk among adults with obstructive and restrictive airway functioning in the United States: a cross-sectional study of the National Health and Nutrition Examination Survey from 2007-2010. Respir Res, 2012. 13: p. 115.

137. Sato, K., et al., Association between plasma adiponectin levels and decline in forced expiratory volume in 1 s in a general Japanese population: the Takahata study. Int J Med Sci, 2014. 11(8): p. 758-64.

138. Wei, Y.F., et al., The impact of metabolic parameters on the change of pulmonary function in obese patients. Surg Obes Relat Dis, 2014. 10(1): p. 23-8.

139. Cirillo, D.J., Y. Agrawal, and P.A. Cassano, Lipids and pulmonary function in the Third National Health and Nutrition Examination Survey. Am J Epidemiol, 2002. 155(9): p. 842-8.

140. Garcia-Larsen, V., et al., Ventilatory function and cardiovascular disease risk factors: a cross-sectional study in young adults. BMC Pulm Med, 2014. 14: p. 206.

141. Naveed, B., et al., Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. Am J Respir Crit Care Med, 2012. 185(4): p. 392-9.

142. Ubhi, B.K., et al., Metabolic profiling detects biomarkers of protein degradation in COPD patients. Eur Respir J, 2012. 40(2): p. 345-55.

143. Kucharska-Newton, A.M., et al., HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study. Lung Cancer, 2008. 61(3): p. 292-300.

144. Ahn, J., et al., Prediagnostic total and high-density lipoprotein cholesterol and risk of cancer. Cancer Epidemiol Biomarkers Prev, 2009. 18(11): p. 2814-21.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

145. Dessi, S., et al., Altered pattern of lipid metabolism in patients with lung cancer. Oncology, 1992. 49(6): p. 436-41.

146. Umeki, S., Decreases in serum cholesterol levels in advanced lung cancer. Respiration, 1993. 60(3): p. 178-81.

147. Fiorenza, A.M., A. Branchi, and D. Sommariva, Serum lipoprotein profile in patients with cancer. A comparison with non-cancer subjects. Int J Clin Lab Res, 2000. 30(3): p. 141-5.

148. Siemianowicz, K., et al., Serum HDL cholesterol concentration in patients with squamous cell and small cell lung cancer. Int J Mol Med, 2000. 6(3): p. 307-11.

149. Chi, P.D., et al., High-density lipoprotein cholesterol is a favorable prognostic factor and negatively correlated with C-reactive protein level in non-small cell lung carcinoma. PLoS One, 2014. 9(3): p. e91080.

150. Rocha, C.M., et al., Metabolic signatures of lung cancer in biofluids: NMR-based metabonomics of blood plasma. J Proteome Res, 2011. 10(9): p. 4314-24.

151. Craig, W.Y., G.E. Palomaki, and J.E. Haddow, Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. BMJ, 1989. 298(6676): p. 784-8.

152. Chelland Campbell, S., R.J. Moffatt, and B.A. Stamford, Smoking and smoking cessation - The relationship between cardiovascular disease and lipoprotein metabolism: a review. Atherosclerosis, 2008. 201(2): p. 225-35.

153. Lavie, L. and P. Lavie, Smoking interacts with sleep apnea to increase cardiovascular risk. Sleep Med, 2008. 9(3): p. 247-53.

154. Jia, E.Z., et al., Smoking and coronary atherosclerosis: follow-up study in China. Clin Exp Pharmacol Physiol, 2009. 36(7): p. 690-5.

155. Lee, Y.C., et al., High-density lipoprotein-cholesterol trajectory pattern, associated lifestyle and biochemical factors among Taiwanese. Circ J, 2009. 73(10): p. 1887-92.

156. De Pergola, G., et al., Free triiodothyronine is associated with smoking habit, independently of obesity, body fat distribution, insulin, and metabolic parameters. J Endocrinol Invest, 2010. 33(11): p. 815-8.

157. Palacios, R., et al., Short communication: contribution of the immunovirological state and traditional cardiovascular risk factors to low HDL-cholesterol in HIV patients. AIDS Res Hum Retroviruses, 2010. 26(11): p. 1167-70.

158. Warner, J.H., et al., Adaptive regression modeling of biomarkers of potential harm in a population of U.S. adult cigarette smokers and nonsmokers. BMC Med Res Methodol, 2010. 10: p. 19.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

159. Costa Silva Zemdegs, J., et al., Lipid profile and cardiovascular risk factors among first-year Brazilian university students in Sao Paulo. Nutr Hosp, 2011. 26(3): p. 553-9.

160. Ghosh, G., et al., Alterations in serum lipid profile patterns in oral squamous cell carcinoma patients. J Contemp Dent Pract, 2011. 12(6): p. 451-6.

161. Zatu, M.C., J.M. Van Rooyen, and A.E. Schutte, Smoking and vascular dysfunction in Africans and Caucasians from South Africa. Cardiovasc J Afr, 2011. 22(1): p. 18-24.

162. Guven, A. and F. Tolun, Effects of smokeless tobacco "Maras powder" use on nitric oxide and cardiovascular risk parameters. Int J Med Sci, 2012. 9(9): p. 786-92.

163. Kralova Lesna, I., et al., HDL and apolipoprotein A1 concentrations as markers of cholesterol efflux in middle-aged women: interaction with smoking. Neuro Endocrinol Lett, 2012. 33 Suppl 2: p. 38-42.

164. Baik, I., et al., A lipoprotein lipase gene polymorphism interacts with consumption of alcohol and unsaturated fat to modulate serum HDL-cholesterol concentrations. J Nutr, 2013. 143(10): p. 1618-25.

165. Nakamura, A., et al., Gene-gene combination effect and interactions among ABCA1, APOA1, SR-B1, and CETP polymorphisms for serum high-density lipoprotein-cholesterol in the Japanese population. PLoS One, 2013. 8(12): p. e82046.

166. Overland, S., et al., Snus use and cardiovascular risk factors in the general population: the HUNT3 study. Addiction, 2013. 108(11): p. 2019-28.

167. Qin, X., et al., Reference intervals for serum lipids in coastal males from Fangchenggang. Clin Lab, 2013. 59(11-12): p. 1289-95.

168. Shahzad, F., S. Tawwab, and U. Ahsan, Lipid profiles of non-diabetic healthy and ischaemic heart disease patients. J Coll Physicians Surg Pak, 2013. 23(4): p. 242-6.

169. Lu, L., et al., Association between salivary cotinine and cardiovascular biomarkers among nonsmokers and current smokers: cross-sectional study of 10,081 participants. Eur J Vasc Endovasc Surg, 2014. 48(6): p. 703-10.

170. Nurjono, M., Y.H. Tay, and J. Lee, The relationship between serum brain-derived neurotrophic factor (BDNF) and cardiometabolic indices in schizophrenia. Schizophr Res, 2014. 157(1-3): p. 244-8.

171. Fatima, F., et al., Comparison of peak expiratory flow rate and lipid profile in asymptomatic smokers and non-smokers. J Ayub Med Coll Abbottabad, 2015. 27(1): p. 55-60.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

172. Roethig, H.J., et al., Population estimates for biomarkers of exposure to cigarette smoke in adult U.S. cigarette smokers. Nicotine Tob Res, 2009. 11(10): p. 1216-25.

173. Forey, B.A., et al., The effect of quitting smoking on HDL-cholesterol - a review based on within-subject changes. Biomarker Research, 2013. 1(1): p. 26.

174. Berlin, I., Endocrine and metabolic effects of smoking cessation. Curr Med Res Opin, 2009. 25(2): p. 527-34.

175. Escola-Gil, J.C., et al., HDL and lifestyle interventions. Handb Exp Pharmacol, 2015. 224: p. 569-92.

176. Suwazono, Y., et al., Longitudinal effect of smoking cessation on physical and laboratory findings. Am J Prev Med, 2010. 38(2): p. 192-200.

177. Korhonen, T., et al., Smoking cessation program with exercise improves cardiovascular disease biomarkers in sedentary women. J Womens Health (Larchmt), 2011. 20(7): p. 1051-64.

178. Rahilly-Tierney, C., et al., Lifestyle change and high-density lipoprotein change: the US Department of Veterans Affairs Normative Aging Study. Clin Cardiol, 2012. 35(7): p. 437-42.

179. Groeneveld, I.F., et al., Sustained body weight reduction by an individual-based lifestyle intervention for workers in the construction industry at risk for cardiovascular disease: results of a randomized controlled trial. Prev Med, 2010. 51(3-4): p. 240-6.

180. Andersen, M.R., et al., Smoking cessation early in pregnancy and birth weight, length, head circumference, and endothelial nitric oxide synthase activity in umbilical and chorionic vessels: an observational study of healthy singleton pregnancies. Circulation, 2009. 119(6): p. 857-64.

181. Rahilly-Tierney, C., et al., Lifestyle changes and 14-year change in high-density lipoprotein cholesterol in a cohort of male physicians. Am Heart J, 2011. 161(4): p. 712-8.

182. Roethig, H.J., et al., A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol, 2008. 48(5): p. 580-91.

183. Martin Leroy, C., et al., Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: a one-month, randomized, ambulatory, controlled clinical study in Poland. Regulatory Toxicology and Pharmacology, 2012. 64; (2 Suppl): p. S74-84.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.2 Appendix 2 Excluded studies from search 1

Literature retrieved using Search 1: To identify articles primarily relevant to the association of HDL-C and smoking and/or smoking cessation using the string: (((((((HDL-C OR high density lipoprotein) AND (smokers OR smoking OR nicotine replacement OR cessation)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language].) AND Humans[Mesh])) NOT Diabetes)) NOT low density

E1. Association of HDL-C with factors other than smoking, MRTPs, or nicotine replacement therapy (NRT)

1. Abbasi, F., et al., *Pioglitazone administration decreases cardiovascular disease risk factors in insulin-resistant smokers.* Metabolism, 2008. **57**(8): p. 1108-14.
2. Aboud, M., et al., *Cardiovascular risk evaluation and antiretroviral therapy effects in an HIV cohort: implications for clinical management: the CREATE 1 study.* Int J Clin Pract, 2010. **64**(9): p. 1252-9.
3. Akbartabartoori, M., M.E. Lean, and C.R. Hankey, *The associations between current recommendation for physical activity and cardiovascular risks associated with obesity.* Eur J Clin Nutr, 2008. **62**(1): p. 1-9.
4. Back, M., et al., *Physical activity in relation to cardiac risk markers in secondary prevention of coronary artery disease.* Int J Cardiol, 2013. **168**(1): p. 478-83.
5. Baker, J., et al., *High-density lipoprotein particles and markers of inflammation and thrombotic activity in patients with untreated HIV infection.* J Infect Dis, 2010. **201**(2): p. 285-92.
6. Baker, J.V., et al., *Untreated HIV infection and large and small artery elasticity.* J Acquir Immune Defic Syndr, 2009. **52**(1): p. 25-31.
7. Benderly, M., V. Boyko, and U. Goldbourt, *Apolipoproteins and long-term prognosis in coronary heart disease patients.* Am Heart J, 2009. **157**(1): p. 103-10.
8. Berger, D., et al., *Alcohol questionnaires and HDL: screening scores as scaled markers of alcohol consumption.* Alcohol, 2013. **47**(6): p. 439-45.
9. Bhuiyan, A.R., et al., *Association of serum bilirubin with pulsatile arterial function in asymptomatic young adults: the Bogalusa Heart Study.* Metabolism, 2008. **57**(5): p. 612-6.
10. Bielemann, R.M., et al., *Longitudinal and cross-sectional associations of physical activity with triglyceride and HDLc levels in young male adults.* J Phys Act Health, 2014. **11**(4): p. 784-9.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

11. Bjerregaard, P., *The association of n-3 fatty acids with serum High Density Cholesterol (HDL) is modulated by sex but not by Inuit ancestry.* Atherosclerosis, 2013. **226**(1): p. 281-5.

12. Buhlin, K., et al., *Periodontal treatment influences risk markers for atherosclerosis in patients with severe periodontitis.* Atherosclerosis, 2009. **206**(2): p. 518-22.

13. Buijsse, B., et al., *Low serum glutathione peroxidase activity is associated with increased cardiovascular mortality in individuals with low HDLc's.* PLoS One, 2012. **7**(6): p. e38901.

14. Camhi, S.M. and P.T. Katzmarzyk, *Differences in body composition between metabolically healthy obese and metabolically abnormal obese adults.* Int J Obes (Lond), 2014. **38**(8): p. 1142-5.

15. Chen, J.D., Y.C. Lin, and S.T. Hsiao, *Obesity and high blood pressure of 12-hour night shift female clean-room workers.* Chronobiol Int, 2010. **27**(2): p. 334-44.

16. Cho, Y.G., et al., *The estimation of cardiovascular risk factors by body mass index and body fat percentage in Korean male adults.* Metabolism, 2009. **58**(6): p. 765-71.

17. Chua, S.K., et al., *Acute ST-elevation myocardial infarction in young patients: 15 years of experience in a single center.* Clin Cardiol, 2010. **33**(3): p. 140-8.

18. Drost, J.T., et al., *Longitudinal analysis of cardiovascular risk parameters in women with a history of hypertensive pregnancy disorders: the Doetinchem Cohort Study.* BJOG, 2013. **120**(11): p. 1333-9.

19. Dunne, M., et al., *Lipid targets in clinical practice: successes, failures and lessons to be learned.* Ir J Med Sci, 2013. **182**(4): p. 673-8.

20. Durand, G., et al., *Firefighters' physical activity: relation to fitness and cardiovascular disease risk.* Med Sci Sports Exerc, 2011. **43**(9): p. 1752-9.

21. Eom, S.Y., et al., *Effects of intronic and exonic polymorphisms of paraoxonase 1 (PON1) gene on serum PON1 activity in a Korean population.* J Korean Med Sci, 2011. **26**(6): p. 720-5.

22. Faeh, D., S. Rohrmann, and J. Braun, *Better risk assessment with glycated hemoglobin instead of cholesterol in CVD risk prediction charts.* Eur J Epidemiol, 2013. **28**(7): p. 551-5.

23. Fessler, M.B., et al., *Relationship between serum cholesterol and indices of erythrocytes and platelets in the US population.* J Lipid Res, 2013. **54**(11): p. 3177-88.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

24. Firtser, S., et al., *Relation of total and free testosterone and sex hormone-binding globulin with cardiovascular risk factors in men aged 24-45 years. The Cardiovascular Risk in Young Finns Study.* Atherosclerosis, 2012. **222**(1): p. 257-62.

25. Gadgil, M.D., et al., *Dietary patterns in Asian Indians in the United States: an analysis of the metabolic syndrome and atherosclerosis in South Asians Living in America study.* J Acad Nutr Diet, 2014. **114**(2): p. 238-43.

26. Gannage-Yared, M.H., R. Chedid, and L. Abs, *Relation between androgens and cardiovascular risk factors in a young population.* Clin Endocrinol (Oxf), 2011. **74**(6): p. 720-5.

27. Garcia-Rios, A., et al., *Genetic variations at ABCG5/G8 genes modulate plasma lipids concentrations in patients with familial hypercholesterolemia.* Atherosclerosis, 2010. **210**(2): p. 486-92.

28. Goldman-Mellor, S., L. Brydon, and A. Steptoe, *Psychological distress and circulating inflammatory markers in healthy young adults.* Psychol Med, 2010. **40**(12): p. 2079-87.

29. Gudmundsdottir, S.L., W.D. Flanders, and L.B. Augestad, *Physical activity and cardiovascular risk factors at menopause: the Nord-Trondelag health study.* Climacteric, 2013. **16**(4): p. 438-46.

30. Guo, Z., et al., *Relationship of the polyunsaturated to saturated fatty acid ratio to cardiovascular risk factors and metabolic syndrome in Japanese: the INTERLIPID study.* J Atheroscler Thromb, 2010. **17**(8): p. 777-84.

31. Hanyu, O., et al., *High-sensitivity CRP reflects insulin resistance in smokers.* J Atheroscler Thromb, 2009. **16**(5): p. 560-7.

32. Hatmi, Z.N., et al., *Relationship between the pattern of coronary artery disease risk factors and lipid ratios with five groups of body mass index in 28566 healthy adults.* Acta Med Iran, 2011. **49**(11): p. 730-6.

33. Hatmi, Z.N., et al., *Trend of lipid ratios associated with well known risk factors of coronary artery disease in different age: a population based study of 31,999 healthy individuals.* Int J Cardiol, 2011. **151**(3): p. 328-32.

34. Hermes, W., et al., *Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study.* Am J Obstet Gynecol, 2013. **208**(6): p. 474 e1-8.

35. Huijgen, R., et al., *Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized, double-blind, controlled trial.* Clin Ther, 2010. **32**(4): p. 615-25.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

36. Imamura, H., et al., *High-density lipoprotein cholesterol subfractions and lecithin: cholesterol acyltransferase activity in collegiate soccer players.* Int J Sports Med, 2013. **34**(5): p. 398-401.

37. Irace, C., et al., *Body mass index, metabolic syndrome and carotid atherosclerosis.* Coron Artery Dis, 2009. **20**(2): p. 94-9.

38. Jaaskelainen, T., et al., *Vitamin D status is associated with sociodemographic factors, lifestyle and metabolic health.* Eur J Nutr, 2013. **52**(2): p. 513-25.

39. Jang, M.J., et al., *Metabolic syndrome is associated with venous thromboembolism in the Korean population.* Arterioscler Thromb Vasc Biol, 2009. **29**(3): p. 311-5.

40. Jensen, M.K., et al., *Alcohol consumption, TaqIB polymorphism of cholesteryl ester transfer protein, high-density lipoprotein cholesterol, and risk of coronary heart disease in men and women.* Eur Heart J, 2008. **29**(1): p. 104-12.

41. Kaneita, Y., et al., *Associations of usual sleep duration with serum lipid and lipoprotein levels.* Sleep, 2008. **31**(5): p. 645-52.

42. Kestila, P., et al., *Socioeconomic status, cardiovascular risk factors, and subclinical atherosclerosis in young adults: the cardiovascular risk in Young Finns Study.* Arterioscler Thromb Vasc Biol, 2012. **32**(3): p. 815-21.

43. Kim, S.Y., et al., *Kale juice improves coronary artery disease risk factors in hypercholesterolemic men.* Biomed Environ Sci, 2008. **21**(2): p. 91-7.

44. Kondo, T., et al., *Multilevel analyses of effects of variation in body mass index on serum lipid concentrations in middle-aged Japanese men.* Nagoya J Med Sci, 2009. **71**(1-2): p. 19-28.

45. Kumar, B.N., et al., *Ethnic differences in SCORE cardiovascular risk in Oslo, Norway.* Eur J Cardiovasc Prev Rehabil, 2009. **16**(2): p. 229-34.

46. Lang, S., et al., *Is impaired kidney function an independent predictor of the risk of myocardial infarction in HIV-infected individuals?* AIDS, 2014. **28**(13): p. 1987-9.

47. Lawlor, D.A., et al., *The association of insulin-like-growth factor 1 (IGF-1) with incident coronary heart disease in women: findings from the prospective British Women's Heart and Health Study.* Atherosclerosis, 2008. **201**(1): p. 198-204.

48. Lee, D.S., et al., *Clinical and genetic correlates of soluble P-selectin in the community.* J Thromb Haemost, 2008. **6**(1): p. 20-31.

49. Lee, H.Y., et al., *Regular exercise training reduces coronary restenosis after percutaneous coronary intervention in patients with acute myocardial infarction.* Int J Cardiol, 2013. **167**(6): p. 2617-22.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

50. Lee, J.Y., et al., *Genetic effects of adiponectin single nucleotide polymorphisms on the clustering of metabolic risk factors in young Korean adults.* Eur J Appl Physiol, 2012. **112**(2): p. 623-9.

51. Lee, Y.W., et al., *The association between intraocular pressure and predictors of coronary heart disease risk in Koreans.* J Korean Med Sci, 2008. **23**(1): p. 31-4.

52. Leino-Arjas, P., et al., *Serum lipids in relation to sciatica among Finns.* Atherosclerosis, 2008. **197**(1): p. 43-9.

53. Li, Y., et al., *Associations of the apolipoprotein A-I gene polymorphism and serum lipid levels in the Guangxi Hei Yi Zhuang and Han populations.* Int J Mol Med, 2008. **21**(6): p. 753-64.

54. Liu, L.Z., E.P. Wu, and H.L. Liu, *Relation between K469E gene polymorphism of ICAM-1 and recurrence of ACS and cardiovascular mortality.* Asian Pac J Trop Med, 2013. **6**(11): p. 916-20.

55. Lopez-Rios, L., et al., *Association of Taq 1B CETP polymorphism with insulin and HOMA levels in the population of the Canary Islands.* Nutr Metab Cardiovasc Dis, 2011. **21**(1): p. 18-24.

56. Magee, G. and P.C. Sharpe, *Paradoxical decreases in high-density lipoprotein cholesterol with fenofibrate: a quite common phenomenon.* J Clin Pathol, 2009. **62**(3): p. 250-3.

57. Maia, D.B., et al., *Abnormal serum lipid profile in Brazilian police officers with post-traumatic stress disorder.* J Affect Disord, 2008. **107**(1-3): p. 259-63.

58. Mansikkaniemi, K., et al., *Cross-sectional associations between physical activity and selected coronary heart disease risk factors in young adults. The Cardiovascular Risk in Young Finns Study.* Ann Med, 2012. **44**(7): p. 733-44.

59. Marques-Vidal, P., et al., *No interaction between alcohol consumption and HDL-related genes on HDL cholesterol levels.* Atherosclerosis, 2010. **211**(2): p. 551-7.

60. Matsuzawa, R., et al., *Association of habitual physical activity measured by an accelerometer with high-density lipoprotein cholesterol levels in maintenance hemodialysis patients.* ScientificWorldJournal, 2013. **2013**: p. 780783.

61. Menotti, A., et al., *Twenty-year cardiovascular and all-cause mortality trends and changes in cardiovascular risk factors in Gubbio, Italy: the role of blood pressure changes.* J Hypertens, 2009. **27**(2): p. 266-74.

62. Miao, L., et al., *Peroxisome proliferator-activated receptor delta +294T > C polymorphism and serum lipid levels in the Guangxi Bai Ku Yao and Han populations.* Lipids Health Dis, 2010. **9**: p. 145.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

63. Mo, X., et al., *Association of lipoprotein lipase polymorphism rs2197089 with serum lipid concentrations and LPL gene expression.* J Hum Genet, 2013. **58**(3): p. 160-4.

64. Mueller, A., et al., *Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals.* J Sex Med, 2010. **7**(9): p. 3190-8.

65. Muhtz, C., et al., *Depressive symptoms and metabolic risk: effects of cortisol and gender.* Psychoneuroendocrinology, 2009. **34**(7): p. 1004-11.

66. Muntoni, S., et al., *Risk factors for cardiovascular disease in Sardinia from 1978 to 2001: a comparative study with Italian mainland.* Eur J Intern Med, 2009. **20**(4): p. 373-7.

67. Nash, S.D., et al., *Long-term variability of inflammatory markers and associated factors in a population-based cohort.* J Am Geriatr Soc, 2013. **61**(8): p. 1269-76.

68. Naumann, E., et al., *The baseline serum lipoprotein profile is related to plant stanol induced changes in serum lipoprotein cholesterol and triacylglycerol concentrations.* J Am Coll Nutr, 2008. **27**(1): p. 117-26.

69. Nettleton, J.A., et al., *Carbohydrate intake modifies associations between ANGPTL4[E40K] genotype and HDL-cholesterol concentrations in White men from the Atherosclerosis Risk in Communities (ARIC) study.* Atherosclerosis, 2009. **203**(1): p. 214-20.

70. Neufingerl, N., M.R. Cobain, and R.S. Newson, *Web-based self-assessment health tools: who are the users and what is the impact of missing input information?* J Med Internet Res, 2014. **16**(9): p. e215.

71. Nishizaki, Y., et al., *Beneficial effects of medical advice provided to elderly persons under the anti-aging health check-up system at Tokai University Tokyo Hospital.* Tokai J Exp Clin Med, 2009. **34**(4): p. 142-51.

72. Onat, A., et al., *Smoking inhibits visceral fat accumulation in Turkish women: relation of visceral fat and body fat mass to atherogenic dyslipidemia, inflammatory markers, insulin resistance, and blood pressure.* Metabolism, 2009. **58**(7): p. 963-70.

73. Peffer, K., et al., *Turbid plasma donations in whole blood donors: fat chance?* Transfusion, 2011. **51**(6): p. 1179-87.

74. Phatak, H., et al., *Prevalence and predictors of lipid abnormalities in patients treated with statins in the UK general practice.* Atherosclerosis, 2009. **202**(1): p. 225-33.

75. Picciotto, S., et al., *Determinants of plasma interleukin-6 levels among survivors of myocardial infarction.* Eur J Cardiovasc Prev Rehabil, 2008. **15**(6): p. 631-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

76. Pop, D., et al., *Role of secretory phospholipase A(2) in women with metabolic syndrome.* Indian J Med Res, 2013. **138**(6): p. 866-72.

77. Real, J.T., et al., *Association of C677T polymorphism in MTHFR gene, high homocysteine and low HDL cholesterol plasma values in heterozygous familial hypercholesterolemia.* J Atheroscler Thromb, 2009. **16**(6): p. 815-20.

78. Rice, M.B., et al., *Acute decrease in HDL cholesterol associated with exposure to welding fumes.* J Occup Environ Med, 2011. **53**(1): p. 17-21.

79. Roef, G.L., et al., *Triiodothyronine and free thyroxine levels are differentially associated with metabolic profile and adiposity-related cardiovascular risk markers in euthyroid middle-aged subjects.* Thyroid, 2014. **24**(2): p. 223-31.

80. Romero-Hidalgo, S., et al., *Carbohydrate intake modulates the effect of the ABCA1-R230C variant on HDL cholesterol concentrations in premenopausal women.* J Nutr, 2012. **142**(2): p. 278-83.

81. Sakakura, K., et al., *Clinical features of early recurrent myocardial infarction.* Heart Vessels, 2009. **24**(5): p. 347-51.

82. Sala, C., et al., *Clinical and functional correlates of platelet cyclic GMP in essential hypertensives.* Am J Hypertens, 2009. **22**(6): p. 674-9.

83. Selvaraj, P. and K.V. Pugalendi, *Anthropometric parameters, lipid peroxidation and antioxidants in auto-rickshaw drivers.* J Basic Clin Physiol Pharmacol, 2009. **20**(4): p. 377-87.

84. Shea, M.K., et al., *Genetic and non-genetic correlates of vitamins K and D.* Eur J Clin Nutr, 2009. **63**(4): p. 458-64.

85. Shon, H.S., et al., *Free T4 is negatively correlated with body mass index in euthyroid women.* Korean J Intern Med, 2008. **23**(2): p. 53-7.

86. Silva, E.F., K.C. Bassichetto, and D.S. Lewi, *Lipid profile, cardiovascular risk factors and metabolic syndrome in a group of AIDS patients.* Arq Bras Cardiol, 2009. **93**(2): p. 113-8.

87. Skoczynska, A., et al., *The dependence between urinary mercury concentration and carotid arterial intima-media thickness in workers occupationally exposed to mercury vapour.* Int J Occup Med Environ Health, 2009. **22**(2): p. 135-42.

88. Steptoe, A., et al., *Distinctive biological correlates of positive psychological well-being in older men and women.* Psychosom Med, 2012. **74**(5): p. 501-8.

89. Sternberg, Z., et al., *Disease modifying therapies modulate cardiovascular risk factors in patients with multiple sclerosis.* Cardiovasc Ther, 2014. **32**(2): p. 33-9.

90. Strandberg, T.E., et al., *Telomere length in old age and cholesterol across the life course.* J Am Geriatr Soc, 2011. **59**(10): p. 1979-81.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

91. Subramanian, S., et al., *Stromal cell-derived factor 1 as a biomarker of heart failure and mortality risk.* Arterioscler Thromb Vasc Biol, 2014. **34**(9): p. 2100-5.

92. Sunto, A., et al., *Serum gamma-GTP activity is closely associated with serum CRP levels in non-overweight and overweight middle-aged Japanese men.* J Nutr Sci Vitaminol (Tokyo), 2013. **59**(2): p. 108-14.

93. Thyagarajan, B., et al., *Factors associated with paraoxonase genotypes and activity in a diverse, young, healthy population: the Coronary Artery Risk Development in Young Adults (CARDIA) study.* Clin Chem, 2008. **54**(4): p. 738-46.

94. Truesdale, K.P., J. Stevens, and J. Cai, *Impact of body mass index levels on lipid abnormalities in Chinese Asians, American Blacks and American Whites: the People's Republic of China (PRC) and Atherosclerosis Risk in Communities (ARIC) Studies.* Atherosclerosis, 2011. **218**(2): p. 517-23.

95. Turner, S.D., et al., *Knowledge-driven multi-locus analysis reveals gene-gene interactions influencing HDL cholesterol level in two independent EMR-linked biobanks.* PLoS One, 2011. **6**(5): p. e19586.

96. Ueda, S., et al., *Serum levels of advanced glycation end products (AGEs) are inversely associated with the number and migratory activity of circulating endothelial progenitor cells in apparently healthy subjects.* Cardiovasc Ther, 2012. **30**(4): p. 249-54.

97. van den Berg, J.F., et al., *Long sleep duration is associated with serum cholesterol in the elderly: the Rotterdam Study.* Psychosom Med, 2008. **70**(9): p. 1005-11.

98. Vemuri, M., et al., *Gender-specific lipid profiles in patients with bipolar disorder.* J Psychiatr Res, 2011. **45**(8): p. 1036-41.

99. Versmissen, J., et al., *A frequent variant in the ABCA1 gene is associated with increased coronary heart disease risk and a better response to statin treatment in familial hypercholesterolemia patients.* Eur Heart J, 2011. **32**(4): p. 469-75.

100. Volpato, S., et al., *High-density lipoprotein cholesterol and objective measures of lower extremity performance in older nondisabled persons: the InChianti study.* J Am Geriatr Soc, 2008. **56**(4): p. 621-9.

101. Wahman, K., et al., *Cardiovascular disease risk and the need for prevention after paraplegia determined by conventional multifactorial risk models: the Stockholm spinal cord injury study.* J Rehabil Med, 2011. **43**(3): p. 237-42.

102. Wakabayashi, I., *Influence of gender on the association of alcohol drinking with blood pressure.* Am J Hypertens, 2008. **21**(12): p. 1310-7.

103. Wakabayashi, I., *Influence of age on the relationship between alcohol consumption and metabolic syndrome.* Gerontology, 2012. **58**(1): p. 24-31.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

104. Wakabayashi, I., *Associations between heavy alcohol drinking and lipid-related indices in middle-aged men.* Alcohol, 2013. **47**(8): p. 637-42.

105. Wu, D.F., et al., *Polymorphism of rs1044925 in the acyl-CoA:cholesterol acyltransferase-1 gene and serum lipid levels in the Guangxi Bai Ku Yao and Han populations.* Lipids Health Dis, 2010. **9**: p. 139.

106. Wu, J., et al., *Hepatic lipase gene -514C/T polymorphism in the Guangxi Hei Yi Zhuang and Han populations.* Lipids, 2008. **43**(8): p. 733-40.

107. Yakob, M., et al., *C-reactive protein in relation to early atherosclerosis and periodontitis.* Clin Oral Investig, 2012. **16**(1): p. 259-65.

108. Zhai, Y., et al., *High sensitivity C-reactive protein associated with different health predictors in middle-aged and oldest old Chinese.* Biomed Environ Sci, 2012. **25**(3): p. 257-66.

E2. HDL-C not associated with risk of disease

1. Aleksandrova, K., et al., *Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European Prospective Investigation into Cancer and Nutrition.* Am J Epidemiol, 2010. **172**(4): p. 407-18.

2. Andriankaja, O.M., et al., *Association between metabolic syndrome and periodontal disease.* Aust Dent J, 2010. **55**(3): p. 252-9.

3. Arai, Y., et al., *Adipose endocrine function, insulin-like growth factor-1 axis, and exceptional survival beyond 100 years of age.* J Gerontol A Biol Sci Med Sci, 2008. **63**(11): p. 1209-18.

4. Bidulescu, A., et al., *Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in African Americans: the Jackson Heart Study.* BMC Cardiovasc Disord, 2013. **13**: p. 9.

5. Bogl, L.H., et al., *Association between habitual dietary intake and lipoprotein subclass profile in healthy young adults.* Nutr Metab Cardiovasc Dis, 2013. **23**(11): p. 1071-8.

6. Cahill, L.E. and A. El-Sohemy, *Vitamin C transporter gene polymorphisms, dietary vitamin C and serum ascorbic acid.* J Nutrigenet Nutrigenomics, 2009. **2**(6): p. 292-301.

7. Camhi, S.M., et al., *Association of metabolic risk with longitudinal physical activity and fitness: coronary artery risk development in young adults (CARDIA).* Metab Syndr Relat Disord, 2013. **11**(3): p. 195-204.

8. Charles-Schoeman, C., et al., *Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis.* Arthritis Rheum, 2009. **60**(10): p. 2870-9.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

9. Colletti, P.M., et al., *Does coronary calcium score predict future cardiac function? Association of subclinical atherosclerosis with left ventricular systolic and diastolic dysfunction at MR imaging in an elderly cohort.* Radiology, 2010. **257**(1): p. 64-70.

10. Cotter, A.G., et al., *High-density lipoprotein levels and 10-year cardiovascular risk in HIV-1-infected patients.* AIDS, 2011. **25**(6): p. 867-9.

11. Davis, K.A., et al., *Racial differences in paraoxonase-1 (PON1): a factor in the health of southerners?* Environ Health Perspect, 2009. **117**(8): p. 1226-31.

12. De Backer, G.G., *New risk markers for cardiovascular prevention.* Curr Atheroscler Rep, 2014. **16**(8): p. 427.

13. Degoma, E.M., et al., *Discordance between non-HDL-cholesterol and LDL-particle measurements: results from the Multi-Ethnic Study of Atherosclerosis.* Atherosclerosis, 2013. **229**(2): p. 517-23.

14. Diaz, F.J., et al., *Possible effects of some antipsychotic drugs on C-reactive protein in a drug-naive psychotic sample.* Schizophr Res, 2010. **121**(1-3): p. 207-12.

15. Engstrom, G., et al., *C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study.* Osteoarthritis Cartilage, 2009. **17**(2): p. 168-73.

16. Fujiwara, S., et al., *S447X polymorphism in the lipoprotein lipase gene and the adiponectin level in the general population: results from the Mima study.* J Atheroscler Thromb, 2009. **16**(3): p. 188-93.

17. Furenes, E.B., et al., *Long-term influence of diet and/or omega-3 fatty acids on matrix metalloproteinase-9 and pregnancy-associated plasma protein-A in men at high risk of coronary heart disease.* Scand J Clin Lab Invest, 2008. **68**(3): p. 177-84.

18. Gotto, A.M., Jr. and J.E. Moon, *Safety of inhibition of cholesteryl ester transfer protein with anacetrapib: the DEFINE study.* Expert Rev Cardiovasc Ther, 2012. **10**(8): p. 955-63.

19. Gupta, H., C.G. Schiros, and T.S. Denney, Jr., *Modified treatment approach using cardiovascular disease risk calculator for primary prevention.* PLoS One, 2014. **9**(8): p. e104478.

20. Gustafsson, S., et al., *Associations of circulating adiponectin with measures of vascular function and morphology.* J Clin Endocrinol Metab, 2010. **95**(6): p. 2927-34.

21. Hall, T.S., et al., *Myeloid-related protein-8/14 and C-reactive protein in individuals evaluated for obstructive sleep apnea.* Sleep Med, 2014. **15**(7): p. 762-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

22. Hamer, M., G.J. Molloy, and E. Stamatakis, *Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms.* J Am Coll Cardiol, 2008. **52**(25): p. 2156-62.

23. He, B.M., S.P. Zhao, and Z.Y. Peng, *Effects of cigarette smoking on HDL quantity and function: implications for atherosclerosis.* J Cell Biochem, 2013. **114**(11): p. 2431-6.

24. Hermsdorff, H.H., et al., *Central adiposity rather than total adiposity measurements are specifically involved in the inflammatory status from healthy young adults.* Inflammation, 2011. **34**(3): p. 161-70.

25. Heroux, M., et al., *Dietary patterns and the risk of mortality: impact of cardiorespiratory fitness.* Int J Epidemiol, 2010. **39**(1): p. 197-209.

26. Hyun, Y.J., et al., *Association of apolipoprotein A5 concentration with serum insulin and triglyceride levels and coronary artery disease in Korean men.* Atherosclerosis, 2009. **205**(2): p. 568-73.

27. Jeppesen, J., et al., *C-reactive protein, insulin resistance and risk of cardiovascular disease: a population-based study.* Eur J Cardiovasc Prev Rehabil, 2008. **15**(5): p. 594-8.

28. Jinjuvadia, R. and S. Liangpunsakul, *Association between metabolic syndrome and its individual components with viral hepatitis B.* Am J Med Sci, 2014. **347**(1): p. 23-7.

29. Joachim, N., et al., *Ethnic variation in early age-related macular degeneration lesions between white Australians and Singaporean Asians.* Invest Ophthalmol Vis Sci, 2014. **55**(7): p. 4421-9.

30. Jolly, K., et al., *The Birmingham Rehabilitation Uptake Maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation.* Heart, 2009. **95**(1): p. 36-42.

31. Junyent, M., et al., *Femoral atherosclerosis in heterozygous familial hypercholesterolemia: influence of the genetic defect.* Arterioscler Thromb Vasc Biol, 2008. **28**(3): p. 580-6.

32. Junyent, M., et al., *The effects of ABCG5/G8 polymorphisms on plasma HDL cholesterol concentrations depend on smoking habit in the Boston Puerto Rican Health Study.* J Lipid Res, 2009. **50**(3): p. 565-73.

33. Kang, H.W., et al., *Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study.* Am J Gastroenterol, 2010. **105**(1): p. 178-87.

34. Karaman, E., et al., *Serum paraoxonase activity and oxidative DNA damage in patients with laryngeal squamous cell carcinoma.* J Craniofac Surg, 2010. **21**(6): p. 1745-9.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

35. Karaolis, M., et al., *Association rule analysis for the assessment of the risk of coronary heart events.* Conf Proc IEEE Eng Med Biol Soc, 2009. **2009**: p. 6238-41.

36. Kawasaki, R., et al., *Prevalence of age-related macular degeneration in a Malay population: the Singapore Malay Eye Study.* Ophthalmology, 2008. **115**(10): p. 1735-41.

37. Khalili, D., et al., *Clinical usefulness of the Framingham cardiovascular risk profile beyond its statistical performance: the Tehran Lipid and Glucose Study.* Am J Epidemiol, 2012. **176**(3): p. 177-86.

38. Kokaze, A., et al., *Difference in effects of cigarette smoking or alcohol consumption on serum non-high-density lipoprotein cholesterol levels is related to mitochondrial DNA 5178 C/A polymorphism in middle-aged Japanese men: a cross-sectional study.* J Physiol Anthropol, 2014. **33**: p. 1.

39. Kushiyama, M., et al., *Relationship between intake of green tea and periodontal disease.* J Periodontol, 2009. **80**(3): p. 372-7.

40. Lee, Y.J., et al., *Association of serum gamma-glutamyltransferase with C-reactive protein levels and white blood cell count in Korean adults.* Clin Chem Lab Med, 2008. **46**(10): p. 1410-5.

41. Lee, Y.J., et al., *Association between serum uric acid and non-alcoholic fatty liver disease in Korean adults.* Clin Chem Lab Med, 2010. **48**(2): p. 175-80.

42. Leon, D.A., et al., *Hazardous alcohol consumption is associated with increased levels of B-type natriuretic peptide: evidence from two population-based studies.* Eur J Epidemiol, 2013. **28**(5): p. 393-404.

43. Marcason, W., *What role does HDL cholesterol have in CVD and what is the most effective way to increase it?* J Am Diet Assoc, 2011. **111**(8): p. 1266.

44. Moallem, S.A., et al., *Correlation between cathepsin D serum concentration and carotid intima-media thickness in hemodialysis patients.* Int Urol Nephrol, 2011. **43**(3): p. 841-8.

45. Murphy, B.M., et al., *Lifestyle and physiological risk factor profiles six weeks after an acute cardiac event: are patients achieving recommended targets for secondary prevention?* Heart Lung Circ, 2011. **20**(7): p. 446-51.

46. Na, H.Y., et al., *Sex differences in the relationship between leukocyte count and chronic kidney disease: the 2007 Korean National Health and Nutrition Examination Survey.* J Womens Health (Larchmt), 2011. **20**(1): p. 99-105.

47. O'Connell, M.D., et al., *Do the effects of testosterone on muscle strength, physical function, body composition, and quality of life persist six months after treatment in intermediate-frail and frail elderly men?* J Clin Endocrinol Metab, 2011. **96**(2): p. 454-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

48. Oda, E. and R. Kawai, *Body mass index is more strongly associated with hypertension than waist circumference in apparently healthy Japanese men and women.* Acta Diabetol, 2010. **47**(4): p. 309-13.

49. Oda, E., R. Kawai, and Y. Aizawa, *Lymphocyte count was significantly associated with hyper-LDL cholesterolemia independently of high-sensitivity C-reactive protein in apparently healthy Japanese.* Heart Vessels, 2012. **27**(4): p. 377-83.

50. Oki, K., et al., *The single nucleotide polymorphism upstream of insulin-induced gene 2 (INSIG2) is associated with the prevalence of hypercholesterolaemia, but not with obesity, in Japanese American women.* Br J Nutr, 2009. **101**(3): p. 322-7.

51. Oliveira, C.P., et al., *Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study.* Int J Cardiol, 2013. **164**(2): p. 221-6.

52. Palmieri, L., et al., *CUORE project: implementation of the 10-year risk score.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(4): p. 642-9.

53. Peterson, G.M., et al., *Cardiovascular risk screening program in Australian community pharmacies.* Pharm World Sci, 2010. **32**(3): p. 373-80.

54. Potter, K., et al., *Homocysteine or renal impairment: which is the real cardiovascular risk factor?* Arterioscler Thromb Vasc Biol, 2008. **28**(6): p. 1158-64.

55. Rahilly-Tierney, C.R., et al., *Apolipoprotein epsilon4 polymorphism does not modify the association between body mass index and high-density lipoprotein cholesterol: a cross-sectional cohort study.* Lipids Health Dis, 2011. **10**: p. 167.

56. Rainwater, D.L., et al., *Determinants of variation in human serum paraoxonase activity.* Heredity (Edinb), 2009. **102**(2): p. 147-54.

57. Rattner, B.P., *In this issue of Epigenetics.* Epigenetics, 2012. **7**(5): p. 419-20.

58. Rye, P.L., et al., *Comparing health behaviours of internal medicine residents and medical students: an observational study.* Clin Invest Med, 2012. **35**(1): p. E40-4.

59. Santiago, F.D., et al., *Protective modulation of carotid atherosclerosis in hyperalphalipoproteinemic individuals.* Int J Cardiovasc Imaging, 2010. **26**(1): p. 27-34.

60. Schottker, B., et al., *Oxidative stress markers and all-cause mortality at older age: a population-based cohort study.* J Gerontol A Biol Sci Med Sci, 2015. **70**(4): p. 518-24.

61. Schwandt, P., T. Bertsch, and G.M. Haas, *Sustained lifestyle advice and cardiovascular risk factors in 687 biological child-parent pairs: the PEP Family Heart Study.* Atherosclerosis, 2011. **219**(2): p. 937-45.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

62. Sekitani, Y., et al., *White blood cell count and cardiovascular biomarkers of atherosclerosis.* Biomarkers, 2010. **15**(5): p. 454-60.

63. Stamatakis, E., et al., *Sedentary time in relation to cardio-metabolic risk factors: differential associations for self-report vs accelerometry in working age adults.* Int J Epidemiol, 2012. **41**(5): p. 1328-37.

64. Sternberg, Z., et al., *The prevalence of the classical and non-classical cardiovascular risk factors in multiple sclerosis patients.* CNS Neurol Disord Drug Targets, 2013. **12**(1): p. 104-11.

65. Stodd, R.T., *The weathervane.* Hawaii J Med Public Health, 2013. **72**(3): p. 110.

66. Sull, J.W., et al., *Serum adiponectin is associated with smoking status in healthy Korean men.* Endocr J, 2009. **56**(1): p. 73-8.

67. Sung, S.H., et al., *White coat hypertension is more risky than prehypertension: important role of arterial wave reflections.* Hypertension, 2013. **61**(6): p. 1346-53.

68. Surtees, P.G., et al., *Educational attainment and mean leukocyte telomere length in women in the European Prospective Investigation into Cancer (EPIC)-Norfolk population study.* Brain Behav Immun, 2012. **26**(3): p. 414-8.

69. Taraboanta, C., et al., *Subclinical atherosclerosis in subjects with family history of premature coronary artery disease.* Am Heart J, 2008. **155**(6): p. 1020-1026 e1.

70. Valacchi, G., et al., *Exploring the link between scavenger receptor B1 expression and chronic obstructive pulmonary disease pathogenesis.* Ann N Y Acad Sci, 2015. **1340**: p. 47-54.

71. van Dis, I., et al., *Do obesity and parental history of myocardial infarction improve cardiovascular risk prediction?* Eur J Prev Cardiol, 2013. **20**(5): p. 793-9.

72. Vasunta, R.L., et al., *High ambulatory blood pressure values associated with non-alcoholic fatty liver in middle-aged adults.* J Hypertens, 2012. **30**(10): p. 2015-9.

73. Wanjia, X., et al., *A high normal TSH level is associated with an atherogenic lipid profile in euthyroid non-smokers with newly diagnosed asymptomatic coronary heart disease.* Lipids Health Dis, 2012. **11**: p. 44.

74. Whitfield, J.B., et al., *Measuring carbohydrate-deficient transferrin by direct immunoassay: factors affecting diagnostic sensitivity for excessive alcohol intake.* Clin Chem, 2008. **54**(7): p. 1158-65.

75. Wiklund, P., et al., *Prolonged breast-feeding protects mothers from later-life obesity and related cardio-metabolic disorders.* Public Health Nutr, 2012. **15**(1): p. 67-74.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

76. Wojas-Krawczyk, K., et al., *The applicability of a predictive index for second- and third-line treatment of unselected non-small-cell lung cancer patients.* Respiration, 2011. **82**(4): p. 341-50.

77. Xie, X., et al., *Serum uric acid levels are associated with polymorphism in the SAA1 gene in Chinese subjects.* PLoS One, 2012. **7**(6): p. e40263.

78. Yannakoulia, M., et al., *Eating patterns may mediate the association between marital status, body mass index, and blood cholesterol levels in apparently healthy men and women from the ATTICA study.* Soc Sci Med, 2008. **66**(11): p.2230-9.

79. Yijiang, Z., et al., *Association of TaqIB polymorphism in the cholesteryl ester transfer protein gene with serum lipid levels in the Guangxi Hei Yi Zhuang and Han populations.* J Investig Med, 2008. **56**(6): p. 847-57.

80. Yla-Herttuala, S., et al., *Stabilization of atherosclerotic plaques: an update.* Eur Heart J, 2013. **34**(42): p. 3251-8.

81. Yu, Y., et al., *Association of variants in the LIPC and ABCA1 genes with intermediate and large drusen and advanced age-related macular degeneration.* Invest Ophthalmol Vis Sci, 2011. **52**(7): p. 4663-70.

82. Yu, Y., et al., *Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models.* Invest Ophthalmol Vis Sci, 2012. **53**(3): p. 1548-56.

83. Zhu, W., et al., *Associations of cardiorespiratory fitness with cardiovascular disease risk factors in middle-aged Chinese women: a cross-sectional study.* BMC Womens Health, 2014. **14**: p. 62.

E3. Association of CVD with factors other than HDL-C

1. Bakhireva, L.N., et al., *Does osteoprotegerin or receptor activator of nuclear factor-kappaB ligand mediate the association between bone and coronary artery calcification?* J Clin Endocrinol Metab, 2008. **93**(5): p. 2009-12.

2. Bloomer, L.D., M.J. Bown, and M. Tomaszewski, *Sexual dimorphism of abdominal aortic aneurysms: a striking example of "male disadvantage" in cardiovascular disease.* Atherosclerosis, 2012. **225**(1): p. 22-8.

3. Caretta, N., et al., *Erectile dysfunction, penile atherosclerosis, and coronary artery vasculopathy in heart transplant recipients.* J Sex Med, 2013. **10**(9): p. 2295-302.

4. Chomistek, A.K., et al., *Vigorous physical activity, mediating biomarkers, and risk of myocardial infarction.* Med Sci Sports Exerc, 2011. **43**(10): p. 1884-90.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

5. Clearfield, M., et al., *The "New Deadly Quartet" for cardiovascular disease in the 21st century: obesity, metabolic syndrome, inflammation and climate change: how does statin therapy fit into this equation?* Curr Atheroscler Rep, 2014. **16**(1): p. 380.

6. Dechering, D.G., et al., *Sphygmomanometric and ambulatory blood pressures as forerunners of carotid and femoral intima-media thickness.* J Hypertens, 2009. **27**(4): p. 813-21.

7. Ehrlich, A.C. and D.A. Smith, *Abdominal diameter index and 12-year cardiovascular disease incidence in male bridge and tunnel workers.* Int J Obes (Lond), 2011. **35**(3): p. 409-15.

8. Grenon, S.M., et al., *Association between n-3 polyunsaturated fatty acid content of red blood cells and inflammatory biomarkers in patients with peripheral artery disease.* J Vasc Surg, 2013. **58**(5): p. 1283-90.

9. Gupta, S.K., et al., *Role of homocysteine & MTHFR C677T gene polymorphism as risk factors for coronary artery disease in young Indians.* Indian J Med Res, 2012. **135**(4): p. 506-12.

10. Gustafsson, S., et al., *Adiponectin and cardiac geometry and function in elderly: results from two community-based cohort studies.* Eur J Endocrinol, 2010. **162**(3): p. 543-50.

11. Herder, M., et al., *Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008.* Arterioscler Thromb Vasc Biol, 2013. **33**(4): p. 858-62.

12. Holmlund, A. and L. Lind, *Number of teeth is related to atherosclerotic plaque in the carotid arteries in an elderly population.* J Periodontol, 2012. **83**(3): p. 287-91.

13. Holtz, J.E., et al., *Mitral annular calcium, inducible myocardial ischemia, and cardiovascular events in outpatients with coronary heart disease (from the Heart and Soul Study).* Am J Cardiol, 2012. **109**(8): p. 1092-6.

14. Holvik, K., et al., *Plasma osteocalcin levels as a predictor of cardiovascular disease in older men and women: a population-based cohort study.* Eur J Endocrinol, 2014. **171**(2): p. 161-70.

15. Honda, C., et al., *Helicobacter pylori infection does not accelerate the age-related progression of arteriosclerosis: a 4-year follow-up study.* J Gastroenterol Hepatol, 2008. **23**(8 Pt 2): p. e373-8.

16. Huang, C.M., et al., *Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities.* J Hypertens, 2011. **29**(3): p. 454-9.

17. Inoue, T., et al., *Elevated resting heart rate is associated with white blood cell count in middle-aged and elderly individuals without apparent cardiovascular disease.* Angiology, 2012. **63**(7): p. 541-6.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

18. Jguirim-Souissi, I., et al., *+294T/C polymorphism in the PPAR-delta gene is associated with risk of coronary artery disease in normolipidemic Tunisians.* Genet Mol Res, 2010. **9**(3): p. 1326-33.

19. Kabir, A.A., et al., *Association between depression and intima-media thickness of carotid bulb in asymptomatic young adults.* Am J Med, 2009. **122**(12): p. 1151 e1-8.

20. Kappelle, P.J., et al., *The plasma leptin/adiponectin ratio predicts first cardiovascular event in men: a prospective nested case-control study.* Eur J Intern Med, 2012. **23**(8): p. 755-9.

21. Khan, Z., et al., *10-Year Framingham risk in patients with retinal vein occlusion: a systematic review and meta-analysis.* Can J Ophthalmol, 2013. **48**(1): p. 40-45 e1.

22. Kodovazenitis, G., et al., *Association between periodontitis and acute myocardial infarction: a case-control study of a nondiabetic population.* J Periodontal Res, 2014. **49**(2): p. 246-52.

23. Kopec, G., et al., *The prevalence of abnormal echocardiographic findings in a sample of urban adult population.* Kardiol Pol, 2014. **72**(1): p. 42-9.

24. Kucharska-Newton, A.M., et al., *HDL-cholesterol and incidence of breast cancer in the ARIC cohort study.* Ann Epidemiol, 2008. **18**(9): p. 671-7.

25. Lee, S.W., et al., *Association between skeletal muscle mass and radial augmentation index in an elderly Korean population.* Arch Gerontol Geriatr, 2014. **59**(1): p. 49-55.

26. Lithander, F.E., et al., *Postprandial effect of dietary fat quantity and quality on arterial stiffness and wave reflection: a randomised controlled trial.* Nutr J, 2013. **12**: p. 93.

27. Liu, Y., et al., *Usefulness of serum cathepsin L as an independent biomarker in patients with coronary heart disease.* Am J Cardiol, 2009. **103**(4): p. 476-81.

28. Lopez-Jornet, P., F. Camacho-Alonso, and M.A. Rodriguez-Martines, *Alterations in serum lipid profile patterns in oral lichen planus: a cross-sectional study.* Am J Clin Dermatol, 2012. **13**(6): p. 399-404.

29. Mao, Y., et al., *Serum gamma-glutamyl transferase: a novel biomarker for coronary artery disease.* Med Sci Monit, 2014. **20**: p. 706-10.

30. Meltzer, M.E., et al., *Low thrombin activatable fibrinolysis inhibitor activity levels are associated with an increased risk of a first myocardial infarction in men.* Haematologica, 2009. **94**(6): p. 811-8.

31. Merriel, S.W., V. Andrews, and C. Salisbury, *Telehealth interventions for primary prevention of cardiovascular disease: a systematic review and meta-analysis.* Prev Med, 2014. **64**: p. 88-95.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

32. Nakata, I., et al., *Association between the cholesteryl ester transfer protein gene and polypoidal choroidal vasculopathy.* Invest Ophthalmol Vis Sci, 2013. **54**(9): p. 6068-73.

33. Onat, A., et al., *Short stature is an independent risk marker for mortality and incident coronary heart disease only in women: a structural relationship?* Anadolu Kardiyol Derg, 2012. **12**(4): p. 289-97.

34. Puri, R., et al., *Antiatherosclerotic effects of long-term maximally intensive statin therapy after acute coronary syndrome: insights from Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin.* Arterioscler Thromb Vasc Biol, 2014. **34**(11): p. 2465-72.

35. Recio-Rodriguez, J.I., et al., *Association of television viewing time with central hemodynamic parameters and the radial augmentation index in adults.* Am J Hypertens, 2013. **26**(4): p. 488-94.

36. Regieli, J.J., et al., *Paraoxonase variants relate to 10-year risk in coronary artery disease: impact of a high-density lipoprotein-bound antioxidant in secondary prevention.* J Am Coll Cardiol, 2009. **54**(14): p. 1238-45.

37. Rockett, F.C., et al., *Cardiovascular disease risk in women with migraine.* J Headache Pain, 2013. **14**: p. 75.

38. Rom Korin, M., et al., *Men's and women's health beliefs differentially predict coronary heart disease incidence in a population-based sample.* Health Educ Behav, 2013. **40**(2): p. 231-9.

39. Sponder, M., et al., *Blood and urine levels of heavy metal pollutants in female and male patients with coronary artery disease.* Vasc Health Risk Manag, 2014. **10**: p. 311-7.

40. Stein, J.M., et al., *Clinical periodontal and microbiologic parameters in patients with acute myocardial infarction.* J Periodontol, 2009. **80**(10): p. 1581-9.

41. Tanaka, S., et al., *Serum levels of thiobarbituric acid-reactive substances are associated with risk of coronary heart disease.* J Atheroscler Thromb, 2011. **18**(7): p. 584-91.

42. Tanno, K., et al., *Associations of marital status with mortality from all causes and mortality from cardiovascular disease in Japanese haemodialysis patients.* Nephrol Dial Transplant, 2013. **28**(4): p. 1013-20.

43. Tzanatos, H.A., et al., *Cardiovascular risk factors in non-diabetic hemodialysis patients: a comparative study.* Ren Fail, 2009. **31**(2): p. 91-7.

44. Tziomalos, K., et al., *Sex-specific differences in cardiovascular risk factors and blood pressure control in hypertensive patients.* J Clin Hypertens (Greenwich), 2014. **16**(4): p. 309-12.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

45. Wang, K.L., et al., *Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality?* J Hypertens, 2009. **27**(3): p. 461-7.

46. Ward, H., et al., *CHD risk in relation to alcohol intake from categorical and open-ended dietary instruments.* Public Health Nutr, 2011. **14**(3): p. 402-9.

47. Xie, X., et al., *Polymorphisms in the SAA1 gene are associated with ankle-to-brachial index in Han Chinese healthy subjects.* Blood Press, 2011. **20**(4): p. 232-8.

48. Zhang, L.N., et al., *Association between polymorphisms of alpha-adducin gene and essential hypertension in Chinese population.* Biomed Res Int, 2013. **2013**: p. 451094.

49. Zhong, W., et al., *Pulse wave velocity and cognitive function in older adults.* Alzheimer Dis Assoc Disord, 2014. **28**(1): p. 44-9.

E4. Metabolic syndrome as the endpoint or the determinant

1. Babio, N., et al., *Adherence to the Mediterranean diet and risk of metabolic syndrome and its components.* Nutr Metab Cardiovasc Dis, 2009. **19**(8): p. 563-70.

2. Bellia, A., et al., *"The Linosa Study": epidemiological and heritability data of the metabolic syndrome in a Caucasian genetic isolate.* Nutr Metab Cardiovasc Dis, 2009. **19**(7): p. 455-61.

3. Fonseca, M.J., et al., *Association between dietary patterns and metabolic syndrome in a sample of Portuguese adults.* Nutr J, 2012. **11**: p. 64.

4. Ge, J.Y., et al., *Elasticity indices of large and small arteries in relation to the metabolic syndrome in Chinese.* Am J Hypertens, 2008. **21**(2): p. 143-7.

5. Ha, C.D., et al., *Association between serum vitamin D status and metabolic syndrome in Korean young men.* Med Sci Sports Exerc, 2014. **46**(3): p. 513-9.

6. Halvorsen, S., et al., *Cardiorespiratory fitness and cardiovascular risk in patients with ankylosing spondylitis: a cross-sectional comparative study.* Arthritis Care Res (Hoboken), 2013. **65**(6): p. 969-76.

7. Han, D.H., et al., *The association of metabolic syndrome with periodontal disease is confounded by age and smoking in a Korean population: the Shiwha-Banwol Environmental Health Study.* J Clin Periodontol, 2010. **37**(7): p. 609-16.

8. Hartley, T.A., et al., *Associations between police officer stress and the metabolic syndrome.* Int J Emerg Ment Health, 2011. **13**(4): p. 243-56.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

9. Hong, D., et al., *Total testosterone and sex hormone-binding globulin are associated with metabolic syndrome independent of age and body mass index in Korean men.* Maturitas, 2013. **74**(2): p. 148-53.

10. Hsu, L.A., et al., *Apolipoprotein A5 gene -1131T/C polymorphism is associated with the risk of metabolic syndrome in ethnic Chinese in Taiwan.* Clin Chem Lab Med, 2008. **46**(12): p. 1714-9.

11. Ingelsson, E., et al., *Circulating ghrelin, leptin, and soluble leptin receptor concentrations and cardiometabolic risk factors in a community-based sample.* J Clin Endocrinol Metab, 2008. **93**(8): p. 3149-57.

12. Jarrett, O.D., et al., *Metabolic syndrome predicts all-cause mortality in persons with human immunodeficiency virus.* AIDS Patient Care STDS, 2013. **27**(5): p. 266-71.

13. Jaunin, J., et al., *Smoking offsets the metabolic benefits of parental longevity in women: the CoLaus study.* Prev Med, 2009. **48**(3): p. 224-31.

14. Jhun, H.J., et al., *Metabolic syndrome in carbon disulfide-poisoned subjects in Korea: does chemical poisoning induce metabolic syndrome?* Int Arch Occup Environ Health, 2009. **82**(7): p. 827-32.

15. Kawada, T., *Predictors of the development of metabolic syndrome in male workers: a 3-year follow-up study.* J Occup Environ Med, 2012. **54**(3): p. 292-5.

16. Kawada, T. and M. Amezawa, *Effects of exercise and serum uric acid on the metabolic syndrome for Japanese workers.* Metab Syndr Relat Disord, 2008. **6**(2): p. 137-41.

17. Kim, M., et al., *Increased oxidative stress in normal-weight postmenopausal women with metabolic syndrome compared with metabolically healthy overweight/obese individuals.* Metabolism, 2013. **62**(4): p. 554-60.

18. Koh, S.B., et al., *Relationships between serum adiponectin with metabolic syndrome and components of metabolic syndrome in non-diabetic Koreans: ARIRANG study.* Yonsei Med J, 2011. **52**(2): p. 234-41.

19. Kwon, Y.E., et al., *The relationship between periodontitis and metabolic syndrome among a Korean nationally representative sample of adults.* J Clin Periodontol, 2011. **38**(9): p. 781-6.

20. Lee, J., et al., *Prevalence of metabolic syndrome among patients with schizophrenia in Singapore.* Ann Acad Med Singapore, 2012. **41**(10): p. 457-62.

21. Lee, K., Y.M. Song, and J. Sung, *Which obesity indicators are better predictors of metabolic risk?: healthy twin study.* Obesity (Silver Spring), 2008. **16**(4): p. 834-40.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

22. Manuck, S.B., et al., *Subjective socioeconomic status and presence of the metabolic syndrome in midlife community volunteers.* Psychosom Med, 2010. **72**(1): p. 35-45.

23. Mirmiran, P., et al., *Magnesium intake and prevalence of metabolic syndrome in adults: Tehran Lipid and Glucose Study.* Public Health Nutr, 2012. **15**(4): p. 693-701.

24. Morita, T., et al., *Association between periodontal disease and metabolic syndrome.* J Public Health Dent, 2009. **69**(4): p. 248-53.

25. Ohrvik, J., et al., *Factor analysis of the individual components of the metabolic syndrome among elderly identifies two factors with different survival patterns--a population-based study.* Metab Syndr Relat Disord, 2009. **7**(3): p. 171-7.

26. Phillips, C.M., et al., *Dietary fat, abdominal obesity and smoking modulate the relationship between plasma complement component 3 concentrations and metabolic syndrome risk.* Atherosclerosis, 2012. **220**(2): p. 513-9.

27. Puustinen, P.J., et al., *Psychological distress predicts the development of the metabolic syndrome: a prospective population-based study.* Psychosom Med, 2011. **73**(2): p. 158-65.

28. Qvarnstrom, M., et al., *Association of salivary lysozyme and C-reactive protein with metabolic syndrome.* J Clin Periodontol, 2010. **37**(9): p. 805-11.

29. Rhee, S.J., et al., *Subjective depressive symptoms and metabolic syndrome among the general population.* Prog Neuropsychopharmacol Biol Psychiatry, 2014. **54**: p. 223-30.

30. Saleem, U., et al., *Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome.* J Clin Endocrinol Metab, 2009. **94**(7): p. 2558-64.

31. Scheers, T., R. Philippaerts, and J. Lefevre, *SenseWear-determined physical activity and sedentary behavior and metabolic syndrome.* Med Sci Sports Exerc, 2013. **45**(3): p. 481-9.

32. Sekita, A., et al., *Elevated depressive symptoms in metabolic syndrome in a general population of Japanese men: a cross-sectional study.* BMC Public Health, 2013. **13**: p. 862.

33. Sirpal, S., *Myeloperoxidase-mediated lipoprotein carbamylation as a mechanistic pathway for atherosclerotic vascular disease.* Clin Sci (Lond), 2009. **116**(9): p. 681-95.

34. Slagter, S.N., et al., *Combined effects of smoking and alcohol on metabolic syndrome: the LifeLines cohort study.* PLoS One, 2014. **9**(4): p. e96406.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

35. Sobieszczyk, M.E., et al., *Prevalence and predictors of metabolic syndrome among HIV-infected and HIV-uninfected women in the Women's Interagency HIV Study*. J Acquir Immune Defic Syndr, 2008. **48**(3): p. 272-80.

36. Suh, S.Y., et al., *The association between normal alanine aminotransferase levels and the metabolic syndrome: 2005 Korean National Health and Nutrition Examination Survey.* Metabolism, 2009. **58**(12): p. 1731-6.

37. Sweileh, W.M., et al., *Prevalence of metabolic syndrome among patients with schizophrenia in Palestine.* BMC Psychiatry, 2012. **12**: p. 235.

38. Tejedor, M.T., et al., *The apolipoprotein E polymorphism rs7412 associates with body fatness independently of plasma lipids in middle aged men.* PLoS One, 2014. **9**(9): p. e108605.

39. Tsai, W.C., et al., *Association of adiponectin with procollagen type I carboxyterminal propeptide in non-diabetic essential hypertension.* Blood Press, 2008. **17**(4): p. 233-8.

40. Vadiveloo, M., N. Parekh, and J. Mattei, *Greater healthful food variety as measured by the US Healthy Food Diversity index is associated with lower odds of metabolic syndrome and its components in US adults.* J Nutr, 2015. **145**(3): p. 564-71.

41. Vanhala, M., et al., *Serum omega-6 polyunsaturated fatty acids and the metabolic syndrome: a longitudinal population-based cohort study.* Am J Epidemiol, 2012. **176**(3): p. 253-60.

42. Wakabayashi, I., *Association between alcohol intake and metabolic syndrome in patients with hypertension.* Clin Exp Hypertens, 2011. **33**(5): p. 299-303.

43. Yamada, Y., et al., *Genetic risk for metabolic syndrome: examination of candidate gene polymorphisms related to lipid metabolism in Japanese people.* J Med Genet, 2008. **45**(1): p. 22-8.

44. Yi, S.M., et al., *Gender-specific association of androgenetic alopecia with metabolic syndrome in a middle-aged Korean population.* Br J Dermatol, 2012. **167**(2): p. 306-13.

45. Zhang, W.H., et al., *Prevalence of metabolic syndrome and its relationship with physical activity in suburban Beijing, China.* Ann Nutr Metab, 2013. **63**(4): p. 298-304.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E5. Association of smoking with CVD

1. Bisanovic, S., B. Mehic, and S. Sivic, *Status of lipids and the frequency diseases of cardiovascular origin in smokers according to the length period of smoking and a number of cigarettes smoked daily.* Bosn J Basic Med Sci, 2011. **11**(1): p. 46-51.

2. Cai, A., et al., *Glycated hemoglobin level is significantly associated with the severity of coronary artery disease in non-diabetic adults.* Lipids Health Dis, 2014. **13**: p. 181.

3. Demirdogen, B.C., et al., *Cytochrome P4501A1 genotypes and smoking- and hypertension-related ischemic stroke risk.* Hum Exp Toxicol, 2013. **32**(5): p. 483-91.

4. Fitch, K.V., et al., *Effects of aging and smoking on carotid intima-media thickness in HIV-infection.* AIDS, 2013. **27**(1): p. 49-57.

5. Funayama, A., et al., *Elevated cystatin C levels predict the incidence of vasospastic angina.* Circ J, 2011. **75**(10): p. 2439-44.

6. Garcia-Rios, A., et al., *Polymorphism at the TRIB1 gene modulates plasma lipid levels: insight from the Spanish familial hypercholesterolemia cohort study.* Nutr Metab Cardiovasc Dis, 2011. **21**(12): p. 957-63.

7. Giudice, R., et al., *Lifestyle-related risk factors, smoking status and cardiovascular disease.* High Blood Press Cardiovasc Prev, 2012. **19**(2): p. 85-92.

8. Ijzelenberg, W., et al., *The effect of a comprehensive lifestyle intervention on cardiovascular risk factors in pharmacologically treated patients with stable cardiovascular disease compared to usual care: a randomised controlled trial.* BMC Cardiovasc Disord, 2012. **12**: p. 71.

9. Ikeya, Y., et al., *Comparison of eicosapentaenoic acid concentrations in plasma between patients with ischemic stroke and control subjects.* Nutrition, 2013. **29**(1): p. 127-31.

10. Karvanen, J. and F.E. Harrell, Jr., *Visualizing covariates in proportional hazards model.* Stat Med, 2009. **28**(14): p. 1957-66.

11. Kashiwagi, Y., et al., *Coronary spastic angina is associated with insulin resistance - possible involvement of endothelial dysfunction.* Coron Artery Dis, 2013. **24**(7): p. 559-65.

12. Kazmierski, R., et al., *Association of atherosclerotic risk factors with carotid adventitial thickness assessed by ultrasonography.* J Clin Ultrasound, 2009. **37**(6): p. 333-41.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

13. Kwiatkowska, W., et al., *Subclinical carotid atherosclerosis and cardiovascular risk factors in HIV-infected patients.* Postepy Hig Med Dosw (Online), 2011. **65**: p. 770-83.

14. Li, S., et al., *Cigarette smoking exacerbates the adverse effects of age and metabolic syndrome on subclinical atherosclerosis: the Bogalusa Heart Study.* PLoS One, 2014. **9**(5): p. e96368.

15. Li, Y., et al., *Decreased serum bilirubin is associated with arterial stiffness in men.* Nutr Metab Cardiovasc Dis, 2013. **23**(4): p. 375-81.

16. Mahrooz, A., et al., *R-carrying genotypes of serum paraoxonase (PON1) 192 polymorphism and higher activity ratio are related to susceptibility against ischemic stroke.* Mol Biol Rep, 2012. **39**(12): p. 11177-85.

17. Marusic, A., K. Belsak, and D. Marusic, *Sensitization of emotions as a risk factor for ischemic heart disease.* Psychiatr Danub, 2008. **20**(1): p. 31-6.

18. McGraw, L.K., et al., *Acute coronary syndromes in deployed military personnel.* J Am Acad Nurse Pract, 2011. **23**(8): p. 427-33.

19. Pannuru, P., et al., *Increased erythrocyte antioxidant status protects against smoking induced hemolysis in moderate smokers.* Hum Exp Toxicol, 2011. **30**(10): p. 1475-81.

20. Priest, J.R., et al., *Self-reported history of childhood smoking is associated with an increased risk for peripheral arterial disease independent of lifetime smoking burden.* PLoS One, 2014. **9**(2): p. e88972.

21. Rejeb, J., et al., *Association of three polymorphisms of scavenger receptor class BI gene (exon8, exon1, intron5) with coronary stenosis in a coronary Tunisian population.* Gene, 2012. **511**(2): p. 383-8.

22. Sandhofer, A., et al., *The influence of two variants in the adenosine triphosphate-binding cassette transporter 1 gene on plasma lipids and carotid atherosclerosis.* Metabolism, 2008. **57**(10): p. 1398-404.

23. Tani, S., et al., *Association of the serum apolipoprotein levels with the occurrence of coronary vasospasm.* Coron Artery Dis, 2011. **22**(3): p. 125-30.

24. Wietlisbach, V., et al., *The relation of body mass index and abdominal adiposity with dyslipidemia in 27 general populations of the WHO MONICA Project.* Nutr Metab Cardiovasc Dis, 2013. **23**(5): p. 432-42.

25. Williams, P.T., *Fifty-three year follow-up of coronary heart disease versus HDL2 and other lipoproteins in Gofman's Livermore Cohort.* J Lipid Res, 2012. **53**(2): p. 266-72.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E6. Association of HDL-C with other diseases/syndromes

1. *Higher HDL levels may help lower your cancer risk. Raising your "good" cholesterol levels appears to have multiple benefits.* Heart Advis, 2010. **13**(9): p. 5.

2. Berard, E., et al., *Cancer mortality according to lipid-lowering drugs and lipoproteins in a general population.* Curr Med Res Opin, 2011. **27**(10): p. 1963-71.

3. Cassani, E., et al., *Cardiometabolic factors and disease duration in patients with Parkinson's disease.* Nutrition, 2013. **29**(11-12): p. 1331-5.

4. Cho, B.J., et al., *Prevalence and risk factors of age-related macular degeneration in Korea: the Korea National Health and Nutrition Examination Survey 2010-2011.* Invest Ophthalmol Vis Sci, 2014. **55**(2): p. 1101-8.

5. Dennis, P.A., et al., *Behavioral health mediators of the link between posttraumatic stress disorder and dyslipidemia.* J Psychosom Res, 2014. **77**(1): p. 45-50.

6. Gasevic, D., et al., *The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort.* Metabolism, 2012. **61**(4): p. 583-9.

7. Ghebranious, N., et al., *A pilot study of gene/gene and gene/environment interactions in Alzheimer disease.* Clin Med Res, 2011. **9**(1): p. 17-25.

8. Heuch, I., et al., *Associations between serum lipid levels and chronic low back pain.* Epidemiology, 2010. **21**(6): p. 837-41.

9. Irace, C., et al., *Influence of blood lipids on plasma and blood viscosity.* Clin Hemorheol Microcirc, 2014. **57**(3): p. 267-74.

10. Kao, W.T., et al., *No change of the lipid profile under the control of ApoE gene polymorphism in schizophrenics under paliperidone treatment.* Psychiatr Q, 2014. **85**(4): p. 487-96.

11. Kim, T., et al., *Association between metabolic syndrome and bone mineral density in Korea: the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV), 2008.* J Bone Miner Metab, 2013. **31**(6): p. 652-62.

12. Klein, R., et al., *The prevalence of age-related macular degeneration and associated risk factors.* Arch Ophthalmol, 2010. **128**(6): p. 750-8.

13. Kopp, J.B., *Rethinking hypertensive kidney disease: arterionephrosclerosis as a genetic, metabolic, and inflammatory disorder.* Curr Opin Nephrol Hypertens, 2013. **22**(3): p. 266-72.

14. Kraemer-Aguiar, L.G., et al., *Microvascular dysfunction: a direct link among BMI, waist circumference and glucose homeostasis in young overweight/obese normoglycemic women?* Int J Obes (Lond), 2010. **34**(1): p. 111-7.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

15. Matsumoto, Y., et al., *Low-molecular-weight adiponectin is more closely associated with episodes of asthma than high-molecular-weight adiponectin.* Endocr J, 2013. **60**(1): p. 119-25.

16. Meek, I.L., et al., *Increased cardiovascular risk factors in different rheumatic diseases compared with the general population.* Rheumatology (Oxford), 2013. **52**(1): p. 210-6.

17. Mondul, A.M., et al., *Serum total and HDL cholesterol and risk of prostate cancer.* Cancer Causes Control, 2011. **22**(11): p. 1545-52.

18. Myers, C.E., et al., *Determinants of retinal venular diameter: the Beaver Dam Eye Study.* Ophthalmology, 2012. **119**(12): p. 2563-71.

19. Trovato, G.M., et al., *Lifestyle interventions, insulin resistance, and renal artery stiffness in essential hypertension.* Clin Exp Hypertens, 2010. **32**(5): p. 262-9.

20. Turan, C., S. Kesebir, and O. Suner, *Are ICAM, VCAM and E-selectin levels different in first manic episode and subsequent remission?* J Affect Disord, 2014. **163**: p. 76-80.

21. Wang, H., et al., *Altered lipid levels in untreated patients with early polymyositis.* PLoS One, 2014. **9**(2): p. e89827.

22. Williams, E., J. Dorn, and C. Crespo, *Prevalence of traditional cardiovascular risk factors in African-American women with systemic lupus erythematosus (SLE): findings from the breakfast with a buddy biomarkers of lupus study.* J Natl Black Nurses Assoc, 2008. **19**(1): p. 26-33.

E7. Association of smoking with other factors or diseases/syndromes

1. Bloom, M.S., et al., *Variability in the components of high-density lipoprotein particles measured in human ovarian follicular fluid: a cross-sectional analysis.* Fertil Steril, 2014. **101**(5): p. 1431-40.

2. Bortolasci, C.C., et al., *Lowered plasma paraoxonase (PON)1 activity is a trait marker of major depression and PON1 Q192R gene polymorphism-smoking interactions differentially predict the odds of major depression and bipolar disorder.* J Affect Disord, 2014. **159**: p. 23-30.

3. Canavan, M., et al., *Vascular risk factors, cardiovascular disease and functional impairment in community-dwelling adults.* Gerontology, 2014. **60**(3): p. 212-21.

4. de Oliveira Fontes Gasperin, L., et al., *Cross-sectional association between cigarette smoking and abdominal obesity among Austrian bank employees.* BMJ Open, 2014. **4**(7): p. e004899.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

5. Frankenfeld, C.L., *Cardiometabolic risk factors are associated with high urinary enterolactone concentration, independent of urinary enterodiol concentration and dietary fiber intake in adults.* J Nutr, 2014. **144**(9): p. 1445-53.

6. Hong, D., et al., *Hair mercury level in smokers and its influence on blood pressure and lipid metabolism.* Environ Toxicol Pharmacol, 2013. **36**(1): p. 103-7.

7. Joehanes, R., et al., *Gene expression analysis of whole blood, peripheral blood mononuclear cells, and lymphoblastoid cell lines from the Framingham Heart Study.* Physiol Genomics, 2012. **44**(1): p. 59-75.

8. Jonasson, F., et al., *Five-year incidence, progression, and risk factors for age-related macular degeneration: the age, gene/environment susceptibility study.* Ophthalmology, 2014. **121**(9): p. 1766-72.

9. Jung, J.G., et al., *Vegetarianism as a protective factor for reflux esophagitis: a retrospective, cross-sectional study between Buddhist priests and general population.* Dig Dis Sci, 2013. **58**(8): p. 2244-52.

10. Kocaman, S.A., et al., *The particular interactions of the traditional cardiovascular risk factors with different circulating specific leukocyte subtype counts in blood: an observational study.* Anadolu Kardiyol Derg, 2011. **11**(7): p. 573-81.

11. Komiyama, M., et al., *Analysis of factors that determine weight gain during smoking cessation therapy.* PLoS One, 2013. **8**(8): p. e72010.

12. Lechanteur, Y.T., et al., *Genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration.* Invest Ophthalmol Vis Sci, 2012. **53**(9): p. 5846-52.

13. Lee, S.H., E. Park, and Y.K. Park, *Glutathione s-transferase m1 and t1 polymorphisms and susceptibility to oxidative damage in healthy korean smokers.* Ann Nutr Metab, 2010. **56**(1): p. 52-8.

14. Lee, Y.J. and I.C. Hwang, *Relationship between serum ferritin level and blood mercury concentration using data from the Korean national health and nutrition examination survey (2010-2012).* Environ Res, 2014. **135**: p. 271-5.

15. Liu, Y., et al., *The characteristics of dyslipidemia patients with different durations in Beijing: a cross-sectional study.* Lipids Health Dis, 2010. **9**: p. 115.

16. Navarro-Compan, V., et al., *Interaction between oxidative stress and smoking is associated with an increased risk of rheumatoid arthritis: a case-control study.* Rheumatology (Oxford), 2013. **52**(3): p. 487-93.

17. Ormseth, M.J., et al., *Association of epicardial adipose tissue with cardiometabolic risk and metabolic syndrome in patients with rheumatoid arthritis.* Arthritis Care Res (Hoboken), 2013. **65**(9): p. 1410-5.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

18. Seo, T., et al., *Interactive effect of paraoxonase-1 Q192R polymorphism and smoking history on the lung function decline in grain workers.* Ann Epidemiol, 2008. **18**(4): p. 330-4.

19. Tognon, G., et al., *Comparison of apolipoprotein (apoB/apoA-I) and lipoprotein (total cholesterol/HDL) ratio determinants. Focus on obesity, diet and alcohol intake.* PLoS One, 2012. **7**(7): p. e40878.

20. Vasunta, R.L., et al., *Nondipping pattern and carotid atherosclerosis in a middle-aged population: OPERA Study.* Am J Hypertens, 2012. **25**(1): p. 60-6.

E8. Neonates, children, or adolescents

1. Ayer, J.G., et al., *Maternal cigarette smoking is associated with reduced high-density lipoprotein cholesterol in healthy 8-year-old children.* Eur Heart J, 2011. **32**(19): p. 2446-53.

2. Camhi, S.M. and P.T. Katzmarzyk, *Prevalence of cardiometabolic risk factor clustering and body mass index in adolescents.* J Pediatr, 2011. **159**(2): p. 303-7.

3. Hujova, Z., et al., *Cardiovascular risk predictors in central Slovakian Roma children and adolescents: regional differences.* Cent Eur J Public Health, 2010. **18**(3): p. 139-44.

4. Hujova, Z., et al., *The prevalence of cigarette smoking and its relation to certain risk predictors of cardiovascular diseases in central-Slovakian Roma children and adolescents.* Cent Eur J Public Health, 2011. **19**(2): p. 67-72.

5. Hujova, Z., J. Desatnikova, and D. Gabor, *Some cardiovascular risk factors in Gypsy children and adolescents from Central Slovakia.* Bratisl Lek Listy, 2009. **110**(4): p. 233-9.

6. Laguna, M., et al., *Heart rate recovery is associated with obesity traits and related cardiometabolic risk factors in children and adolescents.* Nutr Metab Cardiovasc Dis, 2013. **23**(10): p. 995-1001.

7. Magnussen, C.G., et al., *Factors affecting the stability of blood lipid and lipoprotein levels from youth to adulthood: evidence from the Childhood Determinants of Adult Health Study.* Arch Pediatr Adolesc Med, 2011. **165**(1): p. 68-76.

8. Morrison, K.M., et al., *Maternal and pregnancy related predictors of cardiometabolic traits in newborns.* PLoS One, 2013. **8**(2): p. e55815.

9. Neuhauser, H.K., et al., *Prevalence of children with blood pressure measurements exceeding adult cutoffs for optimal blood pressure in Germany.* Eur J Cardiovasc Prev Rehabil, 2009. **16**(2): p. 195-200.

10. Pahkala, K., et al., *Association of physical activity with vascular endothelial function and intima-media thickness.* Circulation, 2011. **124**(18): p. 1956-63.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E9. Environmental tobacco smoke

1. Hirata, K., et al., *Passive smoking is associated with lower serum HDL-C levels in school children.* Pediatr Int, 2010. **52**(2): p. 252-6.
2. Le-Ha, C., et al., *Gender difference in the relationship between passive smoking exposure and HDL-cholesterol levels in late adolescence.* J Clin Endocrinol Metab, 2013. **98**(5): p. 2126-35.
3. Schwandt, P., G.M. Haas, and E. Liepold, *Lifestyle and cardiovascular risk factors in 2001 child-parent pairs: the PEP Family Heart Study.* Atherosclerosis, 2010. **213**(2): p. 642-8.
4. Xie, B., et al., *Environmental tobacco use and indicators of metabolic syndrome in Chinese adults.* Nicotine Tob Res, 2010. **12**(3): p. 198-206.

E10. Association of COPD with other factors

1. Minas, M., et al., *Fetuin-A is associated with disease severity and exacerbation frequency in patients with COPD.* COPD, 2013. **10**(1): p. 28-34.
2. Moreno, J.A., et al., *High-density lipoproteins potentiate alpha1-antitrypsin therapy in elastase-induced pulmonary emphysema.* Am J Respir Cell Mol Biol, 2014. **51**(4): p. 536-49.
3. Rumora, L., et al., *Paraoxonase 1 activity in patients with chronic obstructive pulmonary disease.* COPD, 2014. **11**(5): p. 539-45.

E11. In vitro or animal studies

1. El-Seweidy, M.M., et al., *Nicotine and vascular endothelial dysfunction in female ovariectomized rats: role of estrogen replacement therapy.* J Pharm Pharmacol, 2012. **64**(1): p. 108-19.
2. Hadfield, K.A., et al., *Myeloperoxidase-derived oxidants modify apolipoprotein A-I and generate dysfunctional high-density lipoproteins: comparison of hypothiocyanous acid (HOSCN) with hypochlorous acid (HOCl).* Biochem J, 2013. **449**(2): p. 531-42.
3. Mandraffino, G., et al., *Smoke exposure and circulating progenitor cells: evidence for modulation of antioxidant enzymes and cell count.* Clin Biochem, 2010. **43**(18): p. 1436-42.
4. Naem, E., et al., *Inhibition of apolipoprotein A-I gene by the aryl hydrocarbon receptor: a potential mechanism for smoking-associated hypoalphalipoproteinemia.* Life Sci, 2012. **91**(1-2): p. 64-9.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

5. Sun, L., et al., *Plasma activity of endothelial lipase impacts high-density lipoprotein metabolism and coronary risk factors in humans.* J Atheroscler Thromb, 2014. **21**(4): p. 313-21.

E12. Case studies

1. Pisciotta, L., et al., *A novel mutation of the apolipoprotein A-I gene in a family with familial combined hyperlipidemia.* Atherosclerosis, 2008. **198**(1): p. 145-51.

2. Sucu, M. and V. Davutoglu, *Corneal arcus: an indicator of severe coronary artery disease in a young adult man.* Bratisl Lek Listy, 2009. **110**(12): p. 795.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.3 Appendix 3 Excluded studies from search 2

Literature retrieved using Search 2: To identify articles primarily relevant to the association of HDL-C and CVD using the string: (((((HDL-C OR high density lipoprotein) AND (cardiovascular disease AND association) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language].)) NOT diabetes) NOT low density

E1. Association of HDL-C with factors other than smoking, MRTPs, or nicotine replacement therapy (NRT)

1. Abbasi, F., C. Blasey, and G.M. Reaven, *Cardiometabolic risk factors and obesity: does it matter whether BMI or waist circumference is the index of obesity?* Am J Clin Nutr, 2013. **98**(3): p. 637-40.
2. Abellan, R., et al., *Association of selected ABC gene family single nucleotide polymorphisms with postprandial lipoproteins: results from the population-based Hortega study.* Atherosclerosis, 2010. **211**(1): p. 203-9.
3. Ades, P.A., et al., *The influence of obesity and consequent insulin resistance on coronary risk factors in medically treated patients with coronary disease.* Int J Obes (Lond), 2008. **32**(6): p. 967-74.
4. Ahnstrom, J., et al., *Levels of apolipoprotein M are not associated with the risk of coronary heart disease in two independent case-control studies.* J Lipid Res, 2008. **49**(9): p. 1912-7.
5. Albu, A., et al., *Bone metabolism regulators and arterial stiffness in postmenopausal women.* Maturitas, 2013. **76**(2): p. 146-50.
6. Albuisson, E., et al., *Genetic profiling in healthy subjects from the Stanislas cohort based on 24 polymorphisms: effects on biological variables.* Clin Chem Lab Med, 2008. **46**(1): p. 64-72.
7. Alvim, R.O., et al., *APOE polymorphism is associated with lipid profile, but not with arterial stiffness in the general population.* Lipids Health Dis, 2010. **9**: p. 128.
8. Aptekmann, N.P. and T.B. Cesar, *Orange juice improved lipid profile and blood lactate of overweight middle-aged women subjected to aerobic training.* Maturitas, 2010. **67**(4): p. 343-7.
9. Arias-Santiago, S., et al., *Lipid levels in patients with lichen planus: a case-control study.* J Eur Acad Dermatol Venereol, 2011. **25**(12): p. 1398-401.
10. Arregui, M., et al., *Significant associations of the rs2943634 (2q36.3) genetic polymorphism with adiponectin, high density lipoprotein cholesterol and ischemic stroke.* Gene, 2012. **494**(2): p. 190-5.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

11. Aung, L.H., et al., *Association of the apolipoprotein M gene polymorphisms and serum lipid levels.* Mol Biol Rep, 2013. **40**(2): p. 1843-53.

12. Bahadoran, Z., et al., *Fast food consumption in Iranian adults; dietary intake and cardiovascular risk factors: Tehran Lipid and Glucose Study.* Arch Iran Med, 2012. **15**(6): p. 346-51.

13. Bahrehmand, F., et al., *Matrix metalloproteinase-2 functional promoter polymorphism G1575A is associated with elevated circulatory MMP-2 levels and increased risk of cardiovascular disease in systemic lupus erythematosus patients.* Lupus, 2012. **21**(6): p. 616-24.

14. Bajnok, L., et al., *Relationship of adiponectin to serum paraoxonase 1.* Atherosclerosis, 2008. **197**(1): p. 363-7.

15. Baliarsingh, S., N. Sharma, and R. Mukherjee, *Serum uric acid: marker for atherosclerosis as it is positively associated with "atherogenic index of plasma".* Arch Physiol Biochem, 2013. **119**(1): p. 27-31.

16. Barzi, F., et al., *The discrimination of dyslipidaemia using anthropometric measures in ethnically diverse populations of the Asia-Pacific Region: the Obesity in Asia Collaboration.* Obes Rev, 2010. **11**(2): p. 127-36.

17. Bates, K.A., et al., *Association of cardiovascular factors and Alzheimer's disease plasma amyloid-beta protein in subjective memory complainers.* J Alzheimers Dis, 2009. **17**(2): p. 305-18.

18. Baylin, A., et al., *INSIG2 variants, dietary patterns and metabolic risk in Samoa.* Eur J Clin Nutr, 2013. **67**(1): p. 101-7.

19. Benachour, H., et al., *Association of human cathelicidin (hCAP-18/LL-37) gene expression with cardiovascular disease risk factors.* Nutr Metab Cardiovasc Dis, 2009. **19**(10): p. 720-8.

20. Blasko, I., et al., *Prospective study on association between plasma amyloid beta-42 and atherosclerotic risk factors.* J Neural Transm, 2011. **118**(5): p. 663-72.

21. Bondia-Pons, I., et al., *Isoenergetic diets differing in their n-3 fatty acid and polyphenol content reflect different plasma and HDL-fraction lipidomic profiles in subjects at high cardiovascular risk.* Mol Nutr Food Res, 2014. **58**(9): p. 1873-82.

22. Caglayan, A.O., et al., *Lack of association between the Glu298Asp polymorphism of endothelial nitric oxide synthase and slow coronary flow in the Turkish population.* Can J Cardiol, 2009. **25**(3): p. e69-72.

23. Cao, X.L., et al., *Genetic variant of V825I in the ATP-binding cassette transporter A1 gene and serum lipid levels in the Guangxi Bai Ku Yao and Han populations.* Lipids Health Dis, 2011. **10**: p. 14.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

24. Cappelli, S., et al., *Aortic valve disease and gamma-glutamyltransferase: accumulation in tissue and relationships with calcific degeneration.* Atherosclerosis, 2010. **213**(2): p. 385-91.

25. Carty, C.L., et al., *Association of genetic variation in serum amyloid-A with cardiovascular disease and interactions with IL6, IL1RN, IL1beta and TNF genes in the Cardiovascular Health Study.* J Atheroscler Thromb, 2009. **16**(4): p. 419-30.

26. Carvalho, L.S., et al., *High plasma HDL-C attenuates stress hyperglycemia during acute phase of myocardial infarction.* Atherosclerosis, 2012. **220**(1): p. 231-6.

27. Chan, K.C., et al., *Atorvastatin administration after percutaneous coronary intervention in patients with coronary artery disease and normal lipid profiles: impact on plasma adiponectin level.* Clin Cardiol, 2008. **31**(6): p. 253-8.

28. Chasman, D.I., et al., *Forty-three loci associated with plasma lipoprotein size, concentration, and cholesterol content in genome-wide analysis.* PLoS Genet, 2009. **5**(11): p. e1000730.

29. Chechi, K., et al., *Brown fat like gene expression in the epicardial fat depot correlates with circulating HDL-cholesterol and triglycerides in patients with coronary artery disease.* Int J Cardiol, 2013. **167**(5): p. 2264-70.

30. Chen, E.S., et al., *Association of PPARalpha gene polymorphisms and lipid serum levels in a Brazilian elderly population.* Exp Mol Pathol, 2010. **88**(1): p. 197-201.

31. Chen, W., et al., *Leukocyte telomere length is associated with HDL cholesterol levels: The Bogalusa heart study.* Atherosclerosis, 2009. **205**(2): p. 620-5.

32. Choi, K.M., et al., *Implication of lipocalin-2 and visfatin levels in patients with coronary heart disease.* Eur J Endocrinol, 2008. **158**(2): p. 203-7.

33. Christian, A.H., H. Mochari, and L.J. Mosca, *Waist circumference, body mass index, and their association with cardiometabolic and global risk.* J Cardiometab Syndr, 2009. **4**(1): p. 12-9.

34. Cicero, A.F., et al., *Effect of a sequential training programme on inflammatory, prothrombotic and vascular remodelling biomarkers in hypertensive overweight patients with or without metabolic syndrome.* Eur J Cardiovasc Prev Rehabil, 2009. **16**(6): p. 698-704.

35. Coram, M.A., et al., *Genome-wide characterization of shared and distinct genetic components that influence blood lipid levels in ethnically diverse human populations.* Am J Hum Genet, 2013. **92**(6): p. 904-16.

36. Corsetti, J.P., et al., *Thrombospondin-4 polymorphism (A387P) predicts cardiovascular risk in postinfarction patients with high HDL cholesterol and C-reactive protein levels.* Thromb Haemost, 2011. **106**(6): p. 1170-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

37. Cox, H.C., et al., *Principal component and linkage analysis of cardiovascular risk traits in the Norfolk isolate.* Hum Hered, 2009. **68**(1): p. 55-64.

38. Curti, M.L., et al., *FTO T/A and peroxisome proliferator-activated receptor-gamma Pro12Ala polymorphisms but not ApoA1 -75 are associated with better response to lifestyle intervention in Brazilians at high cardiometabolic risk.* Metab Syndr Relat Disord, 2013. **11**(3): p. 169-76.

39. Dalmeijer, G.W., et al., *Prospective study on dietary intakes of folate, betaine, and choline and cardiovascular disease risk in women.* Eur J Clin Nutr, 2008. **62**(3): p. 386-94.

40. de Carvalho, J.F., et al., *High frequency of lipoprotein risk levels for cardiovascular disease in Takayasu arteritis.* Clin Rheumatol, 2009. **28**(7): p. 801-5.

41. de Carvalho, J.F., et al., *Lack of antilipoprotein lipase antibodies in Takayasu's arteritis.* Clin Dev Immunol, 2009. **2009**: p. 803409.

42. de Carvalho Vidigal, F., et al., *Serum uric acid can predict higher C-reactive protein levels in apparently healthy men.* Nutr Hosp, 2014. **29**(4): p. 935-40.

43. de Goede, J., et al., *Linoleic acid intake, plasma cholesterol and 10-year incidence of CHD in 20,000 middle-aged men and women in the Netherlands.* Br J Nutr, 2012. **107**(7): p. 1070-6.

44. de Jong, H.J., et al., *Alcohol consumption and blood lipids in elderly coronary patients.* Metabolism, 2008. **57**(9): p. 1286-92.

45. DeFilippis, A.P., et al., *Nonalcoholic fatty liver disease and serum lipoproteins: the Multi-Ethnic Study of Atherosclerosis.* Atherosclerosis, 2013. **227**(2): p. 429-36.

46. Deharo, P., et al., *Safety and effectiveness of the association ezetimibe-statin (E-S) versus high dose rosuvastatin after acute coronary syndrome: the SAFE-ES study.* Ann Cardiol Angeiol (Paris), 2014. **63**(4): p. 222-7.

47. Delluc, A., et al., *Lipid parameters, lipid lowering drugs and the risk of venous thromboembolism.* Atherosclerosis, 2012. **220**(1): p. 184-8.

48. Deo, R.C., et al., *Genetic differences between the determinants of lipid profile phenotypes in African and European Americans: the Jackson Heart Study.* PLoS Genet, 2009. **5**(1): p. e1000342.

49. Deshmukh-Taskar, P., et al., *The relationship of breakfast skipping and type of breakfast consumed with overweight/obesity, abdominal obesity, other cardiometabolic risk factors and the metabolic syndrome in young adults. The National Health and Nutrition Examination Survey (NHANES): 1999-2006.* Public Health Nutr, 2013. **16**(11): p. 2073-82.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

50. Dessein, P.H., et al., *Rheumatoid arthritis impacts on the independent relationships between circulating adiponectin concentrations and cardiovascular metabolic risk.* Mediators Inflamm, 2013. **2013**: p. 461849.

51. Djousse, L., et al., *Apolipoprotein e, alcohol consumption, and risk of ischemic stroke: the Framingham Heart Study revisited.* J Stroke Cerebrovasc Dis, 2009. **18**(5): p. 384-8.

52. Dodani, S., et al., *Apo lipoprotein A1 gene polymorphisms predict cardio-metabolic risk in South Asian immigrants.* Dis Markers, 2012. **32**(1): p. 9-19.

53. Dodani, S., et al., *Can dysfunctional HDL explain high coronary artery disease risk in South Asians?* Int J Cardiol, 2008. **129**(1): p. 125-32.

54. Douvris, A., et al., *Functional analysis of the TRIB1 associated locus linked to plasma triglycerides and coronary artery disease.* J Am Heart Assoc, 2014. **3**(3): p. e000884.

55. Dullaart, R.P., et al., *The association of HDL cholesterol concentration with the -629C>A CETP promoter polymorphism is not fully explained by its relationship with plasma cholesteryl ester transfer.* Scand J Clin Lab Invest, 2008. **68**(2): p. 99-105.

56. Ebrahim, S., et al., *Alcohol dehydrogenase type 1C (ADH1C) variants, alcohol consumption traits, HDL-cholesterol and risk of coronary heart disease in women and men: British Women's Heart and Health Study and Caerphilly cohorts.* Atherosclerosis, 2008. **196**(2): p. 871-8.

57. Edmondson, A.C., et al., *Loss-of-function variants in endothelial lipase are a cause of elevated HDL cholesterol in humans.* J Clin Invest, 2009. **119**(4): p. 1042-50.

58. Eilat-Adar, S., et al., *Dietary patterns and their association with cardiovascular risk factors in a population undergoing lifestyle changes: The Strong Heart Study.* Nutr Metab Cardiovasc Dis, 2013. **23**(6): p. 528-35.

59. El-Barbary, A.M., et al., *Association of anti-modified citrullinated vimentin with subclinical atherosclerosis in early rheumatoid arthritis compared with anti-cyclic citrullinated peptide.* J Rheumatol, 2011. **38**(5): p. 828-34.

60. Elshorbagy, A.K., et al., *The association of fasting plasma sulfur-containing compounds with BMI, serum lipids and apolipoproteins.* Nutr Metab Cardiovasc Dis, 2012. **22**(12): p. 1031-8.

61. Enkhmaa, B., et al., *Association of Lp-PLA(2) activity with allele-specific Lp(a) levels in a bi-ethnic population.* Atherosclerosis, 2010. **211**(2): p. 526-30.

62. Enriquez, J.R., et al., *Women tolerate drug therapy for coronary artery disease as well as men do, but are treated less frequently with aspirin, beta-blockers, or statins.* Gend Med, 2008. **5**(1): p. 53-61.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

63. Feng, Y., et al., *Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases.* Atherosclerosis, 2008. **196**(2): p. 590-7.

64. Ferriol, C., et al., *Are there height-dependent differences in subclinical vascular disease in hypertensive patients?* J Clin Hypertens (Greenwich), 2014. **16**(1): p. 70-6.

65. Foldes, G., et al., *Fluvastatin reduces increased blood monocyte Toll-like receptor 4 expression in whole blood from patients with chronic heart failure.* Int J Cardiol, 2008. **124**(1): p. 80-5.

66. Franzini, M., et al., *The calculation of the cardiac troponin T 99th percentile of the reference population is affected by age, gender, and population selection: a multicenter study in Italy.* Clin Chim Acta, 2015. **438**: p. 376-81.

67. Frazier-Wood, A.C., et al., *In cross-sectional observations, dietary quality is not associated with CVD risk in women; in men the positive association is accounted for by BMI.* Br J Nutr, 2015. **113**(8): p. 1244-53.

68. Fu, S., et al., *Prevalence, clinical predictors, and prognostic impact of chronic renal insufficiency in very old Chinese patients with coronary artery disease.* Aging Clin Exp Res, 2013. **25**(4): p. 385-91.

69. Fung, M.M., et al., *Early inflammatory and metabolic changes in association with AGTR1 polymorphisms in prehypertensive subjects.* Am J Hypertens, 2011. **24**(2): p. 225-33.

70. Galan, I., et al., *Alcohol drinking patterns and biomarkers of coronary risk in the Spanish population.* Nutr Metab Cardiovasc Dis, 2014. **24**(2): p. 189-97.

71. Ganguli, D., et al., *Association between inflammatory markers and cardiovascular risk factors in women from Kolkata, W.B, India.* Arq Bras Cardiol, 2011. **96**(1): p. 38-46.

72. Ghatreh Samani, K., et al., *I405V and -629C/A polymorphisms of the cholesteryl ester transfer protein gene in patients with coronary artery disease.* Iran Biomed J, 2009. **13**(2): p. 103-8.

73. Giannessi, D., et al., *Adiponectin is associated with abnormal lipid profile and coronary microvascular dysfunction in patients with dilated cardiomyopathy without overt heart failure.* Metabolism, 2011. **60**(2): p. 227-33.

74. Goh, V.H. and W.G. Hart, *The association of metabolic syndrome and aging with cognition in Asian men.* Aging Male, 2014. **17**(4): p. 216-22.

75. Goutou, M., et al., *AR CAG repeat length is not associated with serum gonadal steroids and lipid levels in healthy men.* Int J Androl, 2009. **32**(6): p. 616-22.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

76. Gray, L., et al., *Parental height in relation to offspring coronary heart disease: examining transgenerational influences on health using the west of Scotland Midspan Family Study.* Int J Epidemiol, 2012. **41**(6): p. 1776-85.

77. Gregoor, J.G., et al., *Association between LEP and LEPR gene polymorphisms and dyslipidemia in patients using atypical antipsychotic medication.* Psychiatr Genet, 2010. **20**(6): p. 311-6.

78. Gulcelik, N.E., et al., *Association of hypoadiponectinemia with metabolic syndrome in patients with polycystic ovary syndrome.* J Natl Med Assoc, 2008. **100**(1): p. 64-8.

79. Guo, Y.J., et al., *The ALDH2 Glu504Lys polymorphism is associated with coronary artery disease in Han Chinese: Relation with endothelial ADMA levels.* Atherosclerosis, 2010. **211**(2): p. 545-50.

80. Gupta, R., et al., *Secular trends in cholesterol lipoproteins and triglycerides and prevalence of dyslipidemias in an urban Indian population.* Lipids Health Dis, 2008. **7**: p. 40.

81. Hamer, M., Y. Chida, and E. Stamatakis, *The role of conventional and novel mechanisms in explaining increased risk of cardiovascular events in offspring with positive parental history.* J Hypertens, 2009. **27**(10): p. 1966-71.

82. Haque, U.J., J.M. Bathon, and J.T. Giles, *Association of vitamin D with cardiometabolic risk factors in rheumatoid arthritis.* Arthritis Care Res (Hoboken), 2012. **64**(10): p. 1497-504.

83. Harman, J.L., et al., *Age is positively associated with high-density lipoprotein cholesterol among African Americans in cross-sectional analysis: the Jackson Heart Study.* J Clin Lipidol, 2011. **5**(3): p. 173-8.

84. Hassanzadeh, T., et al., *Taq1B polymorphism of cholesteryl ester transfer protein (CETP) gene in primary combined hyperlipidaemia.* Indian J Med Res, 2009. **129**(3): p. 293-8.

85. Hilal, Y., et al., *The association of anthropometric measurements and lipid profiles in Turkish hypertensive adults.* Afr Health Sci, 2011. **11**(3): p. 407-13.

86. Hitze, B., et al., *Postprandial triglyceride response in men: role of overweight, abdominal fat and nutrition.* Obes Facts, 2008. **1**(1): p. 45-51.

87. Hiura, Y., et al., *Effects of the Y chromosome on cardiovascular risk factors in Japanese men.* Hypertens Res, 2008. **31**(9): p. 1687-94.

88. Hiura, Y., et al., *Identification of genetic markers associated with high-density lipoprotein-cholesterol by genome-wide screening in a Japanese population: the Suita study.* Circ J, 2009. **73**(6): p. 1119-26.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

89. Holt, R.I., et al., *The relationship between depression, anxiety and cardiovascular disease: findings from the Hertfordshire Cohort Study.* J Affect Disord, 2013. **150**(1): p. 84-90.

90. Hosseinpour-Niazi, S., et al., *Dietary glycemic index, glycemic load, and cardiovascular disease risk factors: Tehran Lipid and Glucose Study.* Arch Iran Med, 2013. **16**(7): p. 401-7.

91. Houston, D.K., et al., *The association between cheese consumption and cardiovascular risk factors among adults.* J Hum Nutr Diet, 2008. **21**(2): p. 129-40.

92. Hsieh, M.C., et al., *Cholesteryl ester transfer protein B1B1 genotype is associated with a parental history of cardiovascular diseases in Taiwanese people.* Med Princ Pract, 2008. **17**(2): p. 143-8.

93. Hulkkonen, J., et al., *Polymorphism in the IL6 promoter region is associated with the risk factors and markers of subclinical atherosclerosis in men: The Cardiovascular Risk in Young Finns Study.* Atherosclerosis, 2009. **203**(2): p. 454-8.

94. Husemoen, L.L., et al., *MTHFR C677T genotype and cardiovascular risk in a general population without mandatory folic acid fortification.* Eur J Nutr, 2014. **53**(7): p. 1549-59.

95. Hyde, C.L., et al., *Genetic association of the CCR5 region with lipid levels in at-risk cardiovascular patients.* Circ Cardiovasc Genet, 2010. **3**(2): p. 162-8.

96. Ikkruthi, S., et al., *Hyperhomocysteinemia and hyperlipoproteinemia (a) in obese South Indian men: an indication for increased cardiovascular risk.* Acta Physiol Hung, 2014. **101**(1): p. 13-20.

97. Imai, A., et al., *Serum cystatin C is associated with early stage coronary atherosclerotic plaque morphology on multidetector computed tomography.* Atherosclerosis, 2011. **218**(2): p. 350-5.

98. Inoue, S., et al., *Step-defined physical activity and cardiovascular risk among middle-aged Japanese: the National Health and Nutrition Survey of Japan 2006.* J Phys Act Health, 2012. **9**(8): p. 1117-24.

99. Irlbeck, T., et al., *Association between single-slice measurements of visceral and abdominal subcutaneous adipose tissue with volumetric measurements: the Framingham Heart Study.* Int J Obes (Lond), 2010. **34**(4): p. 781-7.

100. Issac, M.S., et al., *Association of E-selectin gene polymorphism and serum PAPP-A with carotid atherosclerosis in end-stage renal disease.* Mol Diagn Ther, 2014. **18**(2): p. 243-52.

101. Jenkins, N.T., et al., *Endurance exercise training effects on body fatness, VO2max, HDL-C subfractions, and glucose tolerance are influenced by a PLIN haplotype in older Caucasians.* J Appl Physiol (1985), 2010. **108**(3): p. 498-506.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

102. Jensen, M.K., et al., *The T111I variant in the endothelial lipase gene and risk of coronary heart disease in three independent populations.* Eur Heart J, 2009. **30**(13): p. 1584-9.

103. Jia, E.Z., et al., *Helicobacter pylori infection is associated with decreased serum levels of high density lipoprotein, but not with the severity of coronary atherosclerosis.* Lipids Health Dis, 2009. **8**: p. 59.

104. Johnsson, H., et al., *Analysis and modelling of cholesterol and high-density lipoprotein cholesterol changes across the range of C-reactive protein levels in clinical practice as an aid to better understanding of inflammation-lipid interactions.* Ann Rheum Dis, 2014. **73**(8): p. 1495-9.

105. Kaji, H., et al., *Genetic variations at the CCAAT/enhancer-binding protein delta are associated with metabolic phenotypes in the Japanese population.* Metab Syndr Relat Disord, 2008. **6**(1): p. 24-31.

106. Kalkan, G.Y., et al., *Serum bilirubin level and aortic intima-media thickness in patients without clinical manifestation of atherosclerotic cardiovascular disease.* Angiology, 2014. **65**(4): p. 308-12.

107. Kamezaki, F., et al., *Derivatives of reactive oxygen metabolites correlates with high-sensitivity C-reactive protein.* J Atheroscler Thromb, 2008. **15**(4): p. 206-12.

108. Kardys, I., et al., *Haplotypes of the NR4A2/NURR1 gene and cardiovascular disease: the Rotterdam Study.* Hum Mutat, 2009. **30**(3): p. 417-23.

109. Keenan, T., et al., *Relation of uric acid to serum levels of high-sensitivity C-reactive protein, triglycerides, and high-density lipoprotein cholesterol and to hepatic steatosis.* Am J Cardiol, 2012. **110**(12): p. 1787-92.

110. Kent, S.T., et al., *Sunlight exposure and cardiovascular risk factors in the REGARDS study: a cross-sectional split-sample analysis.* BMC Neurol, 2014. **14**: p. 133.

111. Khan, F., et al., *The association between serum urate levels and arterial stiffness/endothelial function in stroke survivors.* Atherosclerosis, 2008. **200**(2): p. 374-9.

112. Konishi, M., et al., *Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease.* Atherosclerosis, 2010. **209**(2): p. 573-8.

113. Kotani, K., et al., *The association between resistin, high-density lipoprotein cholesterol and carotid atherosclerosis in elderly women with hypertension.* Int J Cardiol, 2010. **141**(2): p. 193-4.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

114. Kotani, K., N. Sakane, and N. Taniguchi, *Association between angiotensin II Type 2 receptor gene A/C3123 polymorphism and high-density lipoprotein cholesterol with hypertension in asymptomatic women.* Med Princ Pract, 2013. **22**(1): p. 65-9.

115. Koupenova, M., et al., *Sex differences in platelet toll-like receptors and their association with cardiovascular risk factors.* Arterioscler Thromb Vasc Biol, 2015. **35**(4): p. 1030-7.

116. Kring, S.I., et al., *Impact of psychological stress on the associations between apolipoprotein E variants and metabolic traits: findings in an American sample of caregivers and controls.* Psychosom Med, 2010. **72**(5): p. 427-33.

117. Lai, Y.H., et al., *Epicardial adipose tissue relating to anthropometrics, metabolic derangements and fatty liver disease independently contributes to serum high-sensitivity C-reactive protein beyond body fat composition: a study validated with computed tomography.* J Am Soc Echocardiogr, 2012. **25**(2): p. 234-41.

118. Lakoski, S.G. and J. Kozlitina, *Ethnic differences in physical activity and metabolic risk: the Dallas Heart Study.* Med Sci Sports Exerc, 2014. **46**(6): p. 1124-32.

119. Lamprea-Montealegre, J.A., et al., *CKD, plasma lipids, and common carotid intima-media thickness: results from the multi-ethnic study of atherosclerosis.* Clin J Am Soc Nephrol, 2012. **7**(11): p. 1777-85.

120. Lanktree, M.B., et al., *Replication of genetic associations with plasma lipoprotein traits in a multiethnic sample.* J Lipid Res, 2009. **50**(7): p. 1487-96.

121. Laurila, P.P., et al., *Genetic association and interaction analysis of USF1 and APOA5 on lipid levels and atherosclerosis.* Arterioscler Thromb Vasc Biol, 2010. **30**(2): p. 346-52.

122. Lavoie, M.E., et al., *Synergistic associations of physical activity and diet quality on cardiometabolic risk factors in overweight and obese postmenopausal women.* Br J Nutr, 2013. **109**(4): p. 605-14.

123. Lee, H.Y., et al., *Regular exercise training reduces coronary restenosis after percutaneous coronary intervention in patients with acute myocardial infarction.* Int J Cardiol, 2013. **167**(6): p. 2617-22.

124. Lee, J.C., et al., *WW-domain-containing oxidoreductase is associated with low plasma HDL-C levels.* Am J Hum Genet, 2008. **83**(2): p. 180-92.

125. Li, C., et al., *Ability of physical activity measurements to assess health-related risks.* Eur J Clin Nutr, 2009. **63**(12): p. 1448-51.

126. Li, F., et al., *Retinol-binding protein 4 as a novel risk factor for cardiovascular disease in patients with coronary artery disease and hyperinsulinemia.* Am J Med Sci, 2014. **348**(6): p. 474-9.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

127. Li, G., et al., *Estimated daily flavonoid and stilbene intake from fruits, vegetables, and nuts and associations with lipid profiles in Chinese adults.* J Acad Nutr Diet, 2013. **113**(6): p. 786-94.

128. Li, Q., X.L. Wei, and R.X. Yin, *Association of ATP binding cassette transporter G8 rs4148217 SNP and serum lipid levels in Mulao and Han nationalities.* Lipids Health Dis, 2012. **11**: p. 46.

129. Li, X.L., et al., *The ratio of high-density lipoprotein cholesterol to apolipoprotein A-I predicts myocardial injury following elective percutaneous coronary intervention.* Clin Cardiol, 2014. **37**(9): p. 558-65.

130. Liang, S., et al., *APOE genotype modifies the association between plasma omega-3 fatty acids and plasma lipids in the Multi-Ethnic Study of Atherosclerosis (MESA).* Atherosclerosis, 2013. **228**(1): p. 181-7.

131. Lin, H., et al., *Variants -250G/A and -514C/T in the LIPC gene are associated with hypertensive disorders of pregnancy in Chinese women.* Genet Mol Res, 2014. **13**(3): p. 6126-34.

132. Liu, P., et al., *Correlation between tongue manifestations and glucose, total cholesterol, and high-density lipoprotein cholesterol in patients with acute cerebral infarction.* J Tradit Chin Med, 2014. **34**(2): p. 162-5.

133. Liu, X., et al., *Determinants of intrathoracic adipose tissue volume and associations with cardiovascular disease risk factors in Amish.* Nutr Metab Cardiovasc Dis, 2014. **24**(3): p. 286-93.

134. Lorenzo, C., et al., *The association of alanine aminotransferase within the normal and mildly elevated range with lipoproteins and apolipoproteins: the Insulin Resistance Atherosclerosis Study.* Diabetologia, 2013. **56**(4): p. 746-57.

135. Lu, C.Q., et al., *Mitochondrial tRNAMet mutation is associated with clinical and biochemical characteristics in primary hypertension.* Mol Med Rep, 2013. **7**(6): p. 1924-8.

136. Luptakova, L., et al., *The association of cytochrome P450 1B1 Leu432Val polymorphism with biological markers of health and menopausal symptoms in Slovak midlife women.* Menopause, 2012. **19**(2): p. 216-24.

137. Ma, L., et al., *Analysis of multiple association studies provides evidence of an expression QTL hub in gene-gene interaction network affecting HDL cholesterol levels.* PLoS One, 2014. **9**(3): p. e92469.

138. Mahemuti, A., et al., *Association of interleukin-6 and C-reactive protein genetic polymorphisms levels with venous thromboembolism.* Chin Med J (Engl), 2012. **125**(22): p. 3997-4002.

139. Mankowska-Cyl, A., et al., *A-FABP and its association with atherogenic risk profile and insulin resistance in young overweight and obese women.* Biomark Med, 2013. **7**(5): p. 723-30.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

140. Martins, C.J., et al., *Association between leptin and its soluble receptor with cardiometabolic risk factors in a Brazilian population.* Eur J Intern Med, 2012. **23**(6): p. e131-5.

141. Mathew, S. and T.M. Chary, *Association of dietary caloric intake with blood pressure, serum lipids and anthropometric indices in patients with hypertension.* Indian J Biochem Biophys, 2013. **50**(5): p. 467-73.

142. Mertens, E., et al., *Cross-sectional study on the relationship between the Mediterranean Diet Score and blood lipids.* Nutr J, 2014. **13**: p. 88.

143. Miksztowicz, V., et al., *Increase in MMP-2 activity in overweight and obese women is associated with menopausal status.* Climacteric, 2012. **15**(6): p. 602-6.

144. Minicocci, I., et al., *Mutations in the ANGPTL3 gene and familial combined hypolipidemia: a clinical and biochemical characterization.* J Clin Endocrinol Metab, 2012. **97**(7): p. E1266-75.

145. Miyoshi, T., et al., *Serum adipocyte fatty acid-binding protein is independently associated with coronary atherosclerotic burden measured by intravascular ultrasound.* Atherosclerosis, 2010. **211**(1): p. 164-9.

146. Mochari-Greenberger, H., et al., *Knowledge, preventive action, and barriers to cardiovascular disease prevention by race and ethnicity in women: an American Heart Association national survey.* J Womens Health (Larchmt), 2010. **19**(7): p. 1243-9.

147. Mok, C.C., et al., *Vitamin D levels in Chinese patients with systemic lupus erythematosus: relationship with disease activity, vascular risk factors and atherosclerosis.* Rheumatology (Oxford), 2012. **51**(4): p. 644-52.

148. Monda, K.L., C.M. Ballantyne, and K.E. North, *Longitudinal impact of physical activity on lipid profiles in middle-aged adults: the Atherosclerosis Risk in Communities Study.* J Lipid Res, 2009. **50**(8): p. 1685-91.

149. Moreira, R.P., et al., *Impact of glucocorticoid receptor gene polymorphisms on the metabolic profile of adult patients with the classical form of 21-hydroxylase deficiency.* PLoS One, 2012. **7**(9): p. e44893.

150. Morra, E.A., et al., *Long-term intense resistance training in men is associated with preserved cardiac structure/function, decreased aortic stiffness, and lower central augmentation pressure.* J Hypertens, 2014. **32**(2): p. 286-93.

151. Myong, J.P., et al., *Association between blood cadmium levels and 10-year coronary heart disease risk in the general Korean population: the Korean National Health and Nutrition Examination Survey 2008-2010.* PLoS One, 2014. **9**(11): p. e111909.

152. Nishida, K., et al., *Induction of hyperadiponectinemia following long-term treatment of patients with rheumatoid arthritis with infliximab (IFX), an anti-TNF-alpha antibody.* Endocr J, 2008. **55**(1): p. 213-6.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

153. Nishimukai, M., et al., *Serum choline plasmalogens, particularly those with oleic acid in sn-2, are associated with proatherogenic state.* J Lipid Res, 2014. **55**(5): p. 956-65.

154. O'Brien, D.M., et al., *A stable isotope biomarker of marine food intake captures associations between n-3 fatty acid intake and chronic disease risk in a Yup'ik study population, and detects new associations with blood pressure and adiponectin.* J Nutr, 2014. **144**(5): p. 706-13.

155. Ohashi, T., et al., *Correlation between circulating adiponectin levels and coronary plaque regression during aggressive lipid-lowering therapy in patients with acute coronary syndrome: subgroup analysis of JAPAN-ACS study.* Atherosclerosis, 2010. **212**(1): p. 237-42.

156. Olinto, M.T., et al., *Major dietary patterns and cardiovascular risk factors among young Brazilian adults.* Eur J Nutr, 2012. **51**(3): p. 281-91.

157. Oliveira, G.B., J.I. Franca, and L.S. Piegas, *Serum adiponectin and cardiometabolic risk in patients with acute coronary syndromes.* Arq Bras Cardiol, 2013. **101**(5): p. 399-409.

158. Padmaja, N., et al., *Cholesteryl ester transfer protein TaqIB, -629C>A and I405V polymorphisms and risk of coronary heart disease in an Indian population.* Clin Chim Acta, 2009. **402**(1-2): p. 139-45.

159. Padmavati, S., U. Gupta, and H.K. Agarwal, *Chronic infections & coronary artery disease with special reference to Chalmydia pneumoniae.* Indian J Med Res, 2012. **135**: p. 228-32.

160. Palacios, C., et al., *Association between adiposity indices and cardiometabolic risk factors among adults living in Puerto Rico.* Public Health Nutr, 2011. **14**(10): p. 1714-23.

161. Parikh, N.I., et al., *Breastfeeding in infancy and adult cardiovascular disease risk factors.* Am J Med, 2009. **122**(7): p. 656-63 e1.

162. Penalvo, J.L. and P. Lopez-Romero, *Urinary enterolignan concentrations are positively associated with serum HDL cholesterol and negatively associated with serum triglycerides in U.S. adults.* J Nutr, 2012. **142**(4): p. 751-6.

163. Peng, Y.S., et al., *Decreased high-density lipoprotein cholesterol is associated with inflammation and insulin resistance in non-diabetic haemodialysis patients.* Nephrology (Carlton), 2010. **15**(7): p. 692-9.

164. Perissinotto, E., et al., *Alcohol consumption and cardiovascular risk factors in older lifelong wine drinkers: the Italian Longitudinal Study on Aging.* Nutr Metab Cardiovasc Dis, 2010. **20**(9): p. 647-55.

165. Peterson, M.D., H.J. Haapala, and E.A. Hurvitz, *Predictors of cardiometabolic risk among adults with cerebral palsy.* Arch Phys Med Rehabil, 2012. **93**(5): p.-816-21.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

166. Phabphal, K. and A. Geater, *The association between BsmI polymorphism and risk factors for atherosclerosis in patients with epilepsy taking valproate.* Seizure, 2013. **22**(9): p. 692-7.

167. Pio-Magalhaes, J.A., et al., *Hip circumference is associated with high density lipoprotein cholesterol response following statin therapy in hypertensive subjects.* J Endocrinol Invest, 2011. **34**(9): p. 680-4.

168. Pollin, T.I., et al., *A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection.* Science, 2008. **322**(5908): p. 1702-5.

169. Rajakumar, C., et al., *Carnitine palmitoyltransferase IA polymorphism P479L is common in Greenland Inuit and is associated with elevated plasma apolipoprotein A-I.* J Lipid Res, 2009. **50**(6): p. 1223-8.

170. Rios-Gonzalez, B.E., et al., *Association of polymorphisms of genes involved in lipid metabolism with blood pressure and lipid values in mexican hypertensive individuals.* Dis Markers, 2014. **2014**: p. 150358.

171. Roos, R., et al., *Effects of an education and home-based pedometer walking program on ischemic heart disease risk factors in people infected with HIV: a randomized trial.* J Acquir Immune Defic Syndr, 2014. **67**(3): p. 268-76.

172. Rubba, F., et al., *Menstrual cycle length, serum lipids and lipoproteins in a cohort of Italian Mediterranean women: findings from Progetto ATENA.* Nutr Metab Cardiovasc Dis, 2008. **18**(10): p. 659-63.

173. Rubin, D., et al., *Postprandial plasma adiponectin decreases after glucose and high fat meal and is independently associated with postprandial triacylglycerols but not with -- 11388 promoter polymorphism.* Br J Nutr, 2008. **99**(1): p. 76-82.

174. Saez, M.E., et al., *WWOX gene is associated with HDL cholesterol and triglyceride levels.* BMC Med Genet, 2010. **11**: p. 148.

175. Sahebkar, A., et al., *A cross-sectional study of the association between heat shock protein 27 antibody titers, pro-oxidant-antioxidant balance and metabolic syndrome in patients with angiographically-defined coronary artery disease.* Clin Biochem, 2011. **44**(17-18): p. 1390-5.

176. Saleh, N., et al., *Homocysteine and other cardiovascular risk factors in patients with lichen planus.* J Eur Acad Dermatol Venereol, 2014. **28**(11): p. 1507-13.

177. Sanchez-Lopez, M., et al., *Leg fat might be more protective than arm fat in relation to lipid profile.* Eur J Nutr, 2013. **52**(2): p. 489-95.

178. Saraswathi, R., et al., *A pilot assessment of oxidative stress byproducts and antioxidant activities among Indian patients with various stages of hypertension.* Clin Exp Hypertens, 2011. **33**(7): p. 437-43.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

179. Sattar, N., et al., *High molecular weight adiponectin is not associated with incident coronary heart disease in older women: a nested prospective case-control study.* J Clin Endocrinol Metab, 2008. **93**(5): p. 1846-9.

180. Schunkert, H., et al., *The correlation between waist circumference and ESC cardiovascular risk score: data from the German metabolic and cardiovascular risk project (GEMCAS).* Clin Res Cardiol, 2008. **97**(11): p. 827-35.

181. Seo, W.K., et al., *C-reactive protein is a predictor of early neurologic deterioration in acute ischemic stroke.* J Stroke Cerebrovasc Dis, 2012. **21**(3): p. 181-6.

182. Sesso, H.D., et al., *Tomato-based food products are related to clinically modest improvements in selected coronary biomarkers in women.* J Nutr, 2012. **142**(2): p. 326-33.

183. Shanker, J., et al., *Genetic studies on the APOA1-C3-A5 gene cluster in Asian Indians with premature coronary artery disease.* Lipids Health Dis, 2008. **7**: p. 33.

184. Shiga, Y., et al., *Significance of plasma levels of pigment epithelium-derived factor as determined by multidetector row computed tomography in patients with mild chronic kidney disease and/or coronary artery disease.* J Int Med Res, 2011. **39**(3): p. 880-90.

185. Shin, H.J., et al., *Instant noodle intake and dietary patterns are associated with distinct cardiometabolic risk factors in Korea.* J Nutr, 2014. **144**(8): p. 1247-55.

186. Shuval, K., et al., *Sedentary behavior, cardiorespiratory fitness, physical activity, and cardiometabolic risk in men: the cooper center longitudinal study.* Mayo Clin Proc, 2014. **89**(8): p. 1052-62.

187. Silva de Almeida, C.C., et al., *What is the meaning of homocysteine in patients on dialysis?* J Ren Nutr, 2011. **21**(5): p. 394-400.

188. Singh, P.P., et al., *Apolipoprotein E polymorphism and its relation to plasma lipids in coronary heart disease.* Indian J Med Sci, 2008. **62**(3): p. 105-12.

189. Smart-Halajko, M.C., et al., *The relationship between plasma angiopoietin-like protein 4 levels, angiopoietin-like protein 4 genotype, and coronary heart disease risk.* Arterioscler Thromb Vasc Biol, 2010. **30**(11): p. 2277-82.

190. Smith, K.M., et al., *Relationship between fish intake, n-3 fatty acids, mercury and risk markers of CHD (National Health and Nutrition Examination Survey 1999-2002).* Public Health Nutr, 2009. **12**(8): p. 1261-9.

191. Son, Y.K., et al., *Association between vascular calcification scores on plain radiographs and fatty acid contents of erythrocyte membrane in hemodialysis patients.* J Ren Nutr, 2012. **22**(1): p. 58-66.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

192. Soreca, I., et al., *Sleep duration is associated with dyslipidemia in patients with bipolar disorder in clinical remission.* J Affect Disord, 2012. **141**(2-3): p. 484-7.

193. Spann, S.J., et al., *The association between childhood trauma and lipid levels in an adult low-income, minority population.* Gen Hosp Psychiatry, 2014. **36**(2): p. 150-5.

194. Spielmann, N., et al., *Cathepsin S genotypes are associated with Apo-A1 and HDL-cholesterol in lean and obese French populations.* Clin Genet, 2008. **74**(2): p. 155-63.

195. Stavropoulos-Kalinoglou, A., et al., *Associations of obesity with modifiable risk factors for the development of cardiovascular disease in patients with rheumatoid arthritis.* Ann Rheum Dis, 2009. **68**(2): p. 242-5.

196. Tabara, Y., et al., *Composition of lower extremity in relation to a high ankle-brachial index.* J Hypertens, 2009. **27**(1): p. 167-73.

197. Tai, E.S., et al., *Polymorphisms at newly identified lipid-associated loci are associated with blood lipids and cardiovascular disease in an Asian Malay population.* J Lipid Res, 2009. **50**(3): p. 514-20.

198. Takeuchi, F., et al., *Confirmation of ALDH2 as a Major locus of drinking behavior and of its variants regulating multiple metabolic phenotypes in a Japanese population.* Circ J, 2011. **75**(4): p. 911-8.

199. Talbot, L.A., A.A. Weinstein, and J.L. Fleg, *Army Physical Fitness Test scores predict coronary heart disease risk in Army National Guard soldiers.* Mil Med, 2009. **174**(3): p. 245-52.

200. Tang, A., J.J. Eng, and A. Krassioukov, *Application of the Sit-Up Test for orthostatic hypotension in individuals with stroke.* Auton Neurosci, 2012. **168**(1-2): p. 82-7.

201. Tang, W., et al., *Associations of lipoprotein lipase gene polymorphisms with longitudinal plasma lipid trends in young adults: The Coronary Artery Risk Development in Young Adults (CARDIA) study.* Circ Cardiovasc Genet, 2010. **3**(2): p. 179-86.

202. Tani, S., et al., *Association of body mass index with coronary plaque regression: 6-month prospective study.* J Atheroscler Thromb, 2009. **16**(3): p. 275-82.

203. Tasdemir, N., et al., *Association of apolipoprotein E genotype and cerebrovascular disease risk factors in a Turkish population.* Int J Neurosci, 2008. **118**(8): p. 1109-29.

204. Tatar, E., et al., *Association of insulin resistance with arterial stiffness in nondiabetic peritoneal dialysis patients.* Int Urol Nephrol, 2012. **44**(1): p. 255-62.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

205. Teng, F., et al., *Interaction between serum uric acid and triglycerides in relation to blood pressure.* J Hum Hypertens, 2011. **25**(11): p. 686-91.

206. Tikhonoff, V., et al., *SAH gene variants revisited in the European Project On Genes in Hypertension.* J Hypertens, 2008. **26**(2): p. 244-50.

207. Todur, S.P. and T.F. Ashavaid, *Association of Sp1 tandem repeat polymorphism of ALOX5 with coronary artery disease in Indian subjects.* Clin Transl Sci, 2012. **5**(5): p. 408-11.

208. Torisu, T., et al., *Possible association of atrophic gastritis and arterial stiffness in healthy middle-aged Japanese.* J Atheroscler Thromb, 2009. **16**(5): p. 691-7.

209. Torriani, M., et al., *Compartmental neck fat accumulation and its relation to cardiovascular risk and metabolic syndrome.* Am J Clin Nutr, 2014. **100**(5): p. 1244-51.

210. Tsai, H.J. and A.C. Tsai, *The association of plasma C-reactive protein levels with anthropometric and lipid parameters in elderly Taiwanese.* Asia Pac J Clin Nutr, 2008. **17**(4): p. 651-6.

211. Tselepis, A.D., et al., *Influence of high-density lipoprotein and paraoxonase-1 on platelet reactivity in patients with acute coronary syndromes receiving clopidogrel therapy.* J Thromb Haemost, 2011. **9**(12): p. 2371-8.

212. Tsiodras, S., et al., *Adherence to Mediterranean diet is favorably associated with metabolic parameters in HIV-positive patients with the highly active antiretroviral therapy-induced metabolic syndrome and lipodystrophy.* Metabolism, 2009. **58**(6): p. 854-9.

213. Tsuchikura, S., et al., *Serum C-reactive protein and thioredoxin levels in subjects with mildly reduced glomerular filtration rate.* BMC Nephrol, 2010. **11**: p. 7.

214. Valentine, P., et al., *Promoting heart health: an HBCU collaboration with the Living Heart Foundation and the National Football League Retired Players Association.* J Natl Med Assoc, 2012. **104**(3-4): p. 186-93.

215. van Eijk, I.C., et al., *Improvement of lipid profile is accompanied by atheroprotective alterations in high-density lipoprotein composition upon tumor necrosis factor blockade: a prospective cohort study in ankylosing spondylitis.* Arthritis Rheum, 2009. **60**(5): p. 1324-30.

216. Vasunilashorn, S., et al., *Apolipoprotein E is associated with blood lipids and inflammation in Taiwanese older adults.* Atherosclerosis, 2011. **219**(1): p. 349-54.

217. Vaverkova, H., et al., *Positive association of adiponectin with soluble vascular cell adhesion molecule sVCAM-1 levels in patients with vascular disease or dyslipidemia.* Atherosclerosis, 2008. **197**(2): p. 725-31.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

218. Vaverkova, H., et al., *Apolipoprotein B versus LDL-cholesterol: Association with other risk factors for atherosclerosis.* Clin Biochem, 2009. **42**(12): p. 1246-51.

219. Verkauskiene, R., et al., *Birth weight and long-term metabolic outcomes: does the definition of smallness matter?* Horm Res, 2008. **70**(5): p. 309-15.

220. Vimaleswaran, K.S., A. Cavadino, and E. Hypponen, *APOA5 genotype influences the association between 25-hydroxyvitamin D and high density lipoprotein cholesterol.* Atherosclerosis, 2013. **228**(1): p. 188-92.

221. Wakabayashi, I., *Influence of age and gender on triglycerides-to-HDL-cholesterol ratio (TG/HDL ratio) and its association with adiposity index.* Arch Gerontol Geriatr, 2012. **55**(3): p. 729-34.

222. Wang, A.Z., et al., *Association of SNP rs17465637 on chromosome 1q41 and rs599839 on 1p13.3 with myocardial infarction in an American caucasian population.* Ann Hum Genet, 2011. **75**(4): p. 475-82.

223. Wang, S.F., et al., *Gender difference in the association of hyperuricemia with hypertension in a middle-aged Chinese population.* Blood Press, 2014. **23**(6): p. 339-44.

224. Wang, X.H., et al., *Plasma levels of omentin-1 and visfatin in senile patients with coronary heart disease and heart failure.* Asian Pac J Trop Med, 2014. **7**(1): p. 55-62.

225. Wang, Y., et al., *Dietary carotenoids are associated with cardiovascular disease risk biomarkers mediated by serum carotenoid concentrations.* J Nutr, 2014. **144**(7): p. 1067-74.

226. Wang, Y., et al., *Association of a functional single-nucleotide polymorphism in the ALDH2 gene with essential hypertension depends on drinking behavior in a Chinese Han population.* J Hum Hypertens, 2013. **27**(3): p. 181-6.

227. Williams, P.T., et al., *Levels of cholesterol in small LDL particles predict atherosclerosis progression and incident CHD in the HDL-Atherosclerosis Treatment Study (HATS).* PLoS One, 2013. **8**(2): p. e56782.

228. Wiltshire, S., et al., *Investigating the association between K198N coding polymorphism in EDN1 and hypertension, lipoprotein levels, the metabolic syndrome and cardiovascular disease.* Hum Genet, 2008. **123**(3): p. 307-13.

229. Woodward, M., et al., *Association between both lipid and protein oxidation and the risk of fatal or non-fatal coronary heart disease in a human population.* Clin Sci (Lond), 2009. **116**(1): p. 53-60.

230. Wu, C., et al., *The human MTHFR rs4846049 polymorphism increases coronary heart disease risk through modifying miRNA binding.* Nutr Metab Cardiovasc Dis, 2013. **23**(7): p. 693-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

231. Wu, D.F., et al., *Sex-specific association of ACAT-1 rs1044925 SNP and serum lipid levels in the hypercholesterolemic subjects.* Lipids Health Dis, 2012. **11**: p. 9.

232. Wu, D.F., et al., *Association between single nucleotide polymorphism rs1044925 and the risk of coronary artery disease and ischemic stroke.* Int J Mol Sci, 2014. **15**(3): p. 3546-59.

233. Wu, D.F., et al., *Scavenger receptor class B type 1 gene rs5888 single nucleotide polymorphism and the risk of coronary artery disease and ischemic stroke: a case-control study.* Int J Med Sci, 2013. **10**(12): p. 1771-7.

234. Wu, D.F., et al., *The SCARB1 rs5888 SNP and serum lipid levels in the Guangxi Mulao and Han populations.* Int J Med Sci, 2012. **9**(8): p. 715-24.

235. Yan, T.T., et al., *Sex-specific association of rs16996148 SNP in the NCAN/CILP2/PBX4 and serum lipid levels in the Mulao and Han populations.* Lipids Health Dis, 2011. **10**: p. 248.

236. Yang, R., et al., *A genome-wide linkage scan identifies multiple quantitative trait loci for HDL-cholesterol levels in families with premature CAD and MI.* J Lipid Res, 2010. **51**(6): p. 1442-51.

237. Yap, R.W., et al., *Association and interaction between dietary pattern and VEGF receptor-2 (VEGFR2) gene polymorphisms on blood lipids in Chinese Malaysian and Japanese adults.* Asia Pac J Clin Nutr, 2012. **21**(2): p. 302-11.

238. Yildiz, A., et al., *The association of serum prolidase activity with the presence and severity of coronary artery disease.* Coron Artery Dis, 2008. **19**(5): p. 319-25.

239. Yin, R.X., et al., *Interactions between the apolipoprotein a1/c3/a5 haplotypes and alcohol consumption on serum lipid levels.* Alcohol Clin Exp Res, 2013. **37**(2): p. 234-43.

240. Zhang, J., et al., *Randomized controlled trial of oatmeal consumption versus noodle consumption on blood lipids of urban Chinese adults with hypercholesterolemia.* Nutr J, 2012. **11**: p. 54.

241. Zhou, J.Y., et al., *Neck circumference as an independent predictive contributor to cardio-metabolic syndrome.* Cardiovasc Diabetol, 2013. **12**: p. 76.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E2. HDL-C not associated with risk of disease

1. Abdel-Azeez, H.A. and M. Al-Zaky, *Plasma osteopontin as a predictor of coronary artery disease: association with echocardiographic characteristics of atherosclerosis.* J Clin Lab Anal, 2010. **24**(3): p. 201-6.

2. Ahmed, W., et al., *Association of ANRIL polymorphism (rs1333049:C>G) with myocardial infarction and its pharmacogenomic role in hypercholesterolemia.* Gene, 2013. **515**(2): p. 416-20.

3. Akadam-Teker, B., et al., *The effects of age and gender on the relationship between HMGCR promoter-911 SNP (rs33761740) and serum lipids in patients with coronary heart disease.* Gene, 2013. **528**(2): p. 93-8.

4. Araujo, L.M., et al., *Association of lipase lipoprotein polymorphisms with high-density lipoprotein and triglycerides in elderly men.* Genet Mol Res, 2010. **9**(1): p. 86-96.

5. Asmathulla, S., et al., *Prevalence of prehypertension and its relationship to cardiovascular disease risk factors in Puducherry.* Indian J Physiol Pharmacol, 2011. **55**(4): p. 343-50.

6. Badiou, S., et al., *Association of non-HDL cholesterol with subclinical atherosclerosis in HIV-positive patients.* J Infect, 2008. **57**(1): p. 47-54.

7. Benn, M., et al., *Nonfasting glucose, ischemic heart disease, and myocardial infarction: a Mendelian randomization study.* J Am Coll Cardiol, 2012. **59**(25): p. 2356-65.

8. Bouhali, T., et al., *Low plasma adiponectin exacerbates the risk of premature coronary artery disease in familial hypercholesterolemia.* Atherosclerosis, 2008. **196**(1): p. 262-9.

9. Bowman, R., et al., *Factor VII, blood lipids and fat intake: gene-nutrient interaction and risk of coronary heart disease with the factor VII R353Q polymorphism.* Eur J Clin Nutr, 2009. **63**(6): p. 771-7.

10. Brunner, N.W., et al., *Impact of insulin resistance on ventricular function in pulmonary arterial hypertension.* J Heart Lung Transplant, 2014. **33**(7): p. 721-6.

11. Buil-Cosiales, P., et al., *Fiber intake and all-cause mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study.* Am J Clin Nutr, 2014. **100**(6): p. 1498-507.

12. Calabresi, L., et al., *Plasma lecithin:cholesterol acyltransferase and carotid intima-media thickness in European individuals at high cardiovascular risk.* J Lipid Res, 2011. **52**(8): p. 1569-74.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

13. Carlsson, C.M., et al., *Increased atherogenic lipoproteins are associated with cognitive impairment: effects of statins and subclinical atherosclerosis.* Alzheimer Dis Assoc Disord, 2009. **23**(1): p. 11-7.

14. Caslake, M.J., et al., *Lipoprotein-associated phospholipase A(2), inflammatory biomarkers, and risk of cardiovascular disease in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).* Atherosclerosis, 2010. **210**(1): p. 28-34.

15. Chen, H., Q. Hua, and H. Hou, *Association of hemoglobin with ambulatory arterial stiffness index in untreated essential hypertensive patients without anemia.* Intern Med, 2011. **50**(22): p. 2759-65.

16. Chen, H.Y., et al., *Triglyceride to high-density lipoprotein cholesterol ratio predicts cardiovascular outcomes in prevalent dialysis patients.* Medicine (Baltimore), 2015. **94**(10): p. e619.

17. Cook, N.R., et al., *Clinical utility of lipoprotein-associated phospholipase A(2) for cardiovascular disease prediction in a multiethnic cohort of women.* Clin Chem, 2012. **58**(9): p. 1352-63.

18. Cruz, W., et al., *Is there a link between inflammation and abnormal lipoprotein profile in Sjogren's syndrome?* Joint Bone Spine, 2010. **77**(3): p. 229-31.

19. Daida, H., et al., *Can intensive lipid-lowering therapy improve the carotid intima-media thickness in Japanese subjects under primary prevention for cardiovascular disease?: The JART and JART extension subanalysis.* J Atheroscler Thromb, 2014. **21**(7): p. 739-54.

20. de Oliveira, E.P., et al., *Dietary, anthropometric, and biochemical determinants of uric acid in free-living adults.* Nutr J, 2013. **12**: p. 11.

21. De Pergola, G., et al., *Arterial hypertension in obesity: relationships with hormone and anthropometric parameters.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(2): p. 240-7.

22. Demirbag, R., et al., *Paraoxonase and arylesterase activities in stent restenosis in bare metal stent.* Coron Artery Dis, 2011. **22**(5): p. 289-93.

23. Demirci, F.Y., et al., *Association of a common G6PC2 variant with fasting plasma glucose levels in non-diabetic individuals.* Ann Nutr Metab, 2010. **56**(1): p. 59-64.

24. Denham, J., et al., *Longer leukocyte telomeres are associated with ultra-endurance exercise independent of cardiovascular risk factors.* PLoS One, 2013. **8**(7): p. e69377.

25. Dorkova, Z., et al., *Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome.* Chest, 2008. **134**(4): p. 686-92.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

26. Emami Razavi, A., et al., *Association between HDL particles size and myeloperoxidase/ paraoxonase-1 (MPO/PON1) ratio in patients with acute coronary syndrome.* Acta Med Iran, 2013. **51**(6): p. 365-71.

27. Feng, L., S.Y. Nian, and J. Zhang, *The GG genotype of telomerase reverse transcriptase at genetic locus rs2736100 is associated with human atherosclerosis risk in the Han Chinese population.* PLoS One, 2014. **9**(1): p. e85719.

28. Ferreira, C.N., et al., *The polymorphism -1131T>C in apolipoprotein A5 gene is associated with dyslipidemia in Brazilian subjects.* Gene, 2013. **516**(1): p. 171-5.

29. Frazier-Wood, A.C., et al., *Genetic variants associated with VLDL, LDL and HDL particle size differ with race/ethnicity.* Hum Genet, 2013. **132**(4): p. 405-13.

30. Fuzikawa, A.K., et al., *Association of ApoE polymorphisms with prevalent hypertension in 1406 older adults: the Bambui Health Aging Study (BHAS).* Braz J Med Biol Res, 2008. **41**(2): p. 89-94.

31. Gambardella, I., et al., *Triglyceride to HDL ratio is a reliable predictor of adverse outcomes in risk stratification for candidates undergoing abdominal aortic surgery.* Eur J Vasc Endovasc Surg, 2011. **41**(2): p. 249-55.

32. Ganna, A., et al., *Risk prediction measures for case-cohort and nested case-control designs: an application to cardiovascular disease.* Am J Epidemiol, 2012. **175**(7): p. 715-24.

33. Garcia-Unciti, M., et al., *Weight-loss diet alone or combined with progressive resistance training induces changes in association between the cardiometabolic risk profile and abdominal fat depots.* Ann Nutr Metab, 2012. **61**(4): p. 296-304.

34. Ghahremanpour, F., et al., *Adipose tissue trans fatty acids and risk of coronary artery disease: a case-control study.* Ann Nutr Metab, 2008. **52**(1): p. 24-8.

35. Golledge, J., et al., *A single-nucleotide polymorphism in the gene encoding osteoprotegerin is associated with diastolic blood pressure in older men.* Am J Hypertens, 2009. **22**(11): p. 1167-70.

36. Gonullu, H., et al., *Serum prolidase enzyme activity and oxidative stress levels in patients with acute hemorrhagic stroke.* Scand J Clin Lab Invest, 2014. **74**(3): p. 199-205.

37. Gonzales, G.F. and V. Tapia, *Increased levels of serum gamma-glutamyltransferase and uric acid on metabolic, hepatic and kidney parameters in subjects at high altitudes.* J Basic Clin Physiol Pharmacol, 2015. **26**(1): p. 81-7.

38. Guaraldi, G., et al., *Hyperhomocysteinaemia in HIV-infected patients: determinants of variability and correlations with predictors of cardiovascular disease.* HIV Med, 2009. **10**(1): p. 28-34.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

39. Guay, S.P., et al., *ABCA1 gene promoter DNA methylation is associated with HDL particle profile and coronary artery disease in familial hypercholesterolemia.* Epigenetics, 2012. **7**(5): p. 464-72.

40. Guay, S.P., D. Gaudet, and D. Brisson, *The g.-469G>A polymorphism in the GPIHBP1 gene promoter is associated with hypertriglyceridemia and has an additive effect on the risk conferred by LPL defective alleles.* Nutr Metab Cardiovasc Dis, 2013. **23**(4): p. 358-65.

41. Hadarits, F., et al., *Stepwise positive association between APOA5 minor allele frequencies and increasing plasma triglyceride quartiles in random patients with hypertriglyceridemia of unclarified origin.* Pathol Oncol Res, 2011. **17**(1): p. 39-44.

42. Hafner, S., et al., *Sleep disturbances and depressed mood: a harmful combination associated with increased leptin levels in women with normal weight.* Biol Psychol, 2012. **89**(1): p. 163-9.

43. Hajas, A., et al., *Vitamin D insufficiency in a large MCTD population.* Autoimmun Rev, 2011. **10**(6): p. 317-24.

44. Hall, S.S., *Genetics: a gene of rare effect.* Nature, 2013. **496**(7444): p. 152-5.

45. Hansen-Krone, I.J., et al., *High fish plus fish oil intake is associated with slightly reduced risk of venous thromboembolism: the Tromso Study.* J Nutr, 2014. **144**(6): p. 861-7.

46. Haybar, H., et al., *Incremental diagnostic value of circulating pentraxin in patients with intermediate risk of coronary artery disease.* Heart, 2013. **99**(9): p. 640-8.

47. Heidema, A.G., et al., *The association of 83 plasma proteins with CHD mortality, BMI, HDL-, and total-cholesterol in men: applying multivariate statistics to identify proteins with prognostic value and biological relevance.* J Proteome Res, 2009. **8**(6): p. 2640-9.

48. Heys, M., et al., *Does childhood meat eating contribute to sex differences in risk factors for ischaemic heart disease in a developing population?* J Epidemiol Community Health, 2011. **65**(6): p. 522-8.

49. Hirose, H., et al., *Cardiac mortality of premature ventricular complexes in healthy people in Japan.* J Cardiol, 2010. **56**(1): p. 23-6.

50. Hla, K.M., et al., *Electrocardiographically indicated cardiovascular disease in sleep-disordered breathing.* Sleep Breath, 2008. **12**(3): p. 251-8.

51. Husemoen, L.L., et al., *The association of ADH and ALDH gene variants with alcohol drinking habits and cardiovascular disease risk factors.* Alcohol Clin Exp Res, 2008. **32**(11): p. 1984-91.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

52. Inoue, M., et al., *Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan.* Eur J Cancer Prev, 2009. **18**(3): p. 240-7.

53. Itani, O., et al., *Association of onset of obesity with sleep duration and shift work among Japanese adults.* Sleep Med, 2011. **12**(4): p. 341-5.

54. Ivey, K.L., et al., *Association between yogurt, milk, and cheese consumption and common carotid artery intima-media thickness and cardiovascular disease risk factors in elderly women.* Am J Clin Nutr, 2011. **94**(1): p. 234-9.

55. Jensky, N.E., et al., *The association of bone density and calcified atherosclerosis is stronger in women without dyslipidemia: the multi-ethnic study of atherosclerosis.* J Bone Miner Res, 2011. **26**(11): p. 2702-9.

56. Jovicic, S., et al., *Association of lipid and inflammatory markers with C-reactive protein in cardiovascular risk assessment for primary prevention.* Clin Lab, 2009. **55**(11-12): p. 411-9.

57. Kaess, B.M., et al., *FGF21 signalling pathway and metabolic traits - genetic association analysis.* Eur J Hum Genet, 2010. **18**(12): p. 1344-8.

58. Kaestner, S., et al., *Lack of association between the cholesteryl ester transfer protein gene--TaqIB polymorphism and coronary restenosis following percutaneous transluminal coronary angioplasty and stenting: a pilot study.* Angiology, 2010. **61**(4): p. 338-43.

59. Kasai, T., et al., *Mortality risk of triglyceride levels in patients with coronary artery disease.* Heart, 2013. **99**(1): p. 22-9.

60. Kaya, H., et al., *Association between neutrophil to lymphocyte ratio and severity of coronary artery disease.* Clin Appl Thromb Hemost, 2014. **20**(1): p. 50-4.

61. Kazmierski, R., et al., *Association of atherosclerotic risk factors with carotid adventitial thickness assessed by ultrasonography.* J Clin Ultrasound, 2009. **37**(6): p. 333-41.

62. Kitamura, A., et al., *Association between non-high-density lipoprotein cholesterol levels and the incidence of coronary heart disease among Japanese: the Circulatory Risk in Communities Study (CIRCS).* J Atheroscler Thromb, 2011. **18**(6): p. 454-63.

63. Kofler, B.M., et al., *Apolipoprotein E genotype and the cardiovascular disease risk phenotype: impact of sex and adiposity (the FINGEN study).* Atherosclerosis, 2012. **221**(2): p. 467-70.

64. Kotani, K., K. Tsuzaki, and N. Sakane, *Paraoxonase-1 gene Q192R polymorphism and reactive oxygen metabolites.* J Int Med Res, 2012. **40**(4): p. 1513-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

65. Kramer, C.K., et al., *A prospective study of abdominal obesity and coronary artery calcium progression in older adults.* J Clin Endocrinol Metab, 2009. **94**(12): p. 5039-44.

66. Kwon, S., *Association between abdominal obesity and cardiovascular risk factors in normal-weight Korean women.* Health Care Women Int, 2009. **30**(5): p. 447-52.

67. Lamon-Fava, S., et al., *Lipoprotein(a) levels, apo(a) isoform size, and coronary heart disease risk in the Framingham Offspring Study.* J Lipid Res, 2011. **52**(6): p. 1181-7.

68. Lamprea-Montealegre, J.A., et al., *Chronic kidney disease, plasma lipoproteins, and coronary artery calcium incidence: the Multi-Ethnic Study of Atherosclerosis.* Arterioscler Thromb Vasc Biol, 2013. **33**(3): p. 652-8.

69. Lehtimaki, T., et al., *Adult-type hypolactasia is not a predisposing factor for the early functional and structural changes of atherosclerosis: the Cardiovascular Risk in Young Finns Study.* Clin Sci (Lond), 2008. **115**(9): p. 265-71.

70. Leuschen, J., et al., *Association of statin use with cataracts: a propensity score-matched analysis.* JAMA Ophthalmol, 2013. **131**(11): p. 1427-34.

71. Li, X., et al., *Association of apolipoprotein A5 gene promoter region -1131T>C with risk of stroke in Han Chinese.* Eur J Intern Med, 2011. **22**(1): p. 99-102.

72. Lipkowitz, M.S., et al., *Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans.* Kidney Int, 2013. **83**(1): p. 114-20.

73. Liu, S.J., et al., *Fatty acid desaturase 1 polymorphisms are associated with coronary heart disease in a Chinese population.* Chin Med J (Engl), 2012. **125**(5): p. 801-6.

74. Lublinghoff, N., et al., *Genetic variants of the promoter of the heme oxygenase-1 gene and their influence on cardiovascular disease (the Ludwigshafen Risk and Cardiovascular Health study).* BMC Med Genet, 2009. **10**: p. 36.

75. Luboshitzky, R., et al., *Cardiovascular risk factors in primary hyperparathyroidism.* J Endocrinol Invest, 2009. **32**(4): p. 317-21.

76. McClure, C.K., et al., *Lactation and maternal subclinical cardiovascular disease among premenopausal women.* Am J Obstet Gynecol, 2012. **207**(1): p. 46 e1-8.

77. Meltzer, M.E., et al., *Reduced plasma fibrinolytic capacity as a potential risk factor for a first myocardial infarction in young men.* Br J Haematol, 2009. **145**(1): p. 121-7.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

78. Nair, D., et al., *Association of total cholesterol/ high-density lipoprotein cholesterol ratio with proximal coronary atherosclerosis detected by multislice computed tomography.* Prev Cardiol, 2009. **12**(1): p. 19-26.

79. Nakamura, T., et al., *Rapid stabilization of vulnerable carotid plaque within 1 month of pitavastatin treatment in patients with acute coronary syndrome.* J Cardiovasc Pharmacol, 2008. **51**(4): p. 365-71.

80. Nassar, B.A., et al., *Role of the fractalkine receptor CX3CR1 polymorphisms V249I and T280M as risk factors for early-onset coronary artery disease in patients with no classic risk factors.* Scand J Clin Lab Invest, 2008. **68**(4): p. 286-91.

81. Ninomiya, T., et al., *Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: the Hisayama Study.* Atherosclerosis, 2013. **231**(2): p. 261-7.

82. Olesnevich, M.E., et al., *Serum ferritin levels associated with increased risk for developing CHD in a low-income urban population.* Public Health Nutr, 2012. **15**(7): p. 1291-8.

83. Ong, K.L., et al., *Association of a polymorphism in the lipin 1 gene with systolic blood pressure in men.* Am J Hypertens, 2008. **21**(5): p. 539-45.

84. Ou, Z., et al., *The genetic polymorphisms of cathepsin S were associated with metabolic disorders in a Chinese Han population.* Gene, 2013. **526**(2): p. 385-9.

85. Ozdol, S., S. Sahin, and L. Tokgozoglu, *Xanthelasma palpebrarum and its relation to atherosclerotic risk factors and lipoprotein (a).* Int J Dermatol, 2008. **47**(8): p. 785-9.

86. Pan, L., G. Lu, and Z. Chen, *Combined use of apolipoprotein B/apolipoprotein A1 ratio and non-high-density lipoprotein cholesterol before routine clinical lipid measurement in predicting coronary heart disease.* Coron Artery Dis, 2014. **25**(5): p. 433-8.

87. Panichi, V., et al., *Geriatric nutritional risk index is a strong predictor of mortality in hemodialysis patients: data from the Riscavid cohort.* J Nephrol, 2014. **27**(2): p. 193-201.

88. Pare, G., et al., *Effect of PON1 Q192R genetic polymorphism on clopidogrel efficacy and cardiovascular events in the Clopidogrel in the Unstable Angina to Prevent Recurrent Events trial and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events.* Circ Cardiovasc Genet, 2012. **5**(2): p. 250-6.

89. Peng, D.Q., et al., *Increased soluble OX40L is associated with carotid intima-media thickness.* Clin Lab, 2010. **56**(9-10): p. 449-57.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

90. Pillois, X., et al., *TaqIB polymorphism in cholesterol ester transfer protein (CETP) gene predicts future cardiovascular death in patients experiencing an acute coronary syndrome.* Clin Chem Lab Med, 2009. **47**(9): p. 1039-46.

91. Pounis, G., et al., *Dietary patterns and fatty acids levels of three European populations. Results from the IMMIDIET study.* Nutr Metab Cardiovasc Dis, 2014. **24**(8): p. 883-90.

92. Qureischie, H., et al., *Association of CETP polymorphisms with the risk of vascular dementia and white matter lesions.* J Neural Transm, 2009. **116**(4): p. 467-72.

93. Raichlin, E., et al., *Lipoprotein-associated phospholipase A2 predicts progression of cardiac allograft vasculopathy and increased risk of cardiovascular events in heart transplant patients.* Transplantation, 2008. **85**(7): p. 963-8.

94. Rajapurkar, M.M., et al., *Association of catalytic iron with cardiovascular disease.* Am J Cardiol, 2012. **109**(3): p. 438-42.

95. Rao, V.U., et al., *An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy.* Arthritis Rheumatol, 2015. **67**(2): p. 372-80.

96. Raslova, K., et al., *Association of metabolic and genetic factors with cholesterol esterification rate in HDL plasma and atherogenic index of plasma in a 40 years old Slovak population.* Physiol Res, 2011. **60**(5): p. 785-95.

97. Rasmussen-Torvik, L.J., et al., *Demographic and cardiovascular risk factors modify association of fasting insulin with incident coronary heart disease and ischemic stroke (from the Atherosclerosis Risk In Communities Study).* Am J Cardiol, 2010. **105**(10): p. 1420-5.

98. Rebhi, L., et al., *5' ins/del and 3' VNTR polymorphisms in the apolipoprotein B gene in relation to lipids and coronary artery disease.* Clin Chem Lab Med, 2008. **46**(3): p. 329-34.

99. Robbins, C.L., et al., *Cholesterol screening for women: who is "at-risk"?* J Womens Health (Larchmt), 2013. **22**(5): p. 404-11.

100. Romundstad, P.R., et al., *Hypertension in pregnancy and later cardiovascular risk: common antecedents?* Circulation, 2010. **122**(6): p. 579-84.

101. Rosenau, B.J., K.H. Costenbader, and P.H. Schur, *C-reactive protein, anti C-reactive protein antibodies and clinical atherosclerosis.* Vasc Med, 2008. **13**(1): p. 25-8.

102. Ryan, J.M., et al., *Habitual physical activity and cardiometabolic risk factors in adults with cerebral palsy.* Res Dev Disabil, 2014. **35**(9): p. 1995-2002.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

103. Saleh, F., et al., *Phytoestrogen intake and cardiovascular risk markers in Bangladeshi postmenopausal women.* Mymensingh Med J, 2011. **20**(2): p. 219-25.

104. Sancini, A., et al., *Cardiovascular risk in rotogravure industry.* J Occup Environ Med, 2012. **54**(5): p. 551-7.

105. Santo, A.S., et al., *Postprandial lipemia detects the effect of soy protein on cardiovascular disease risk compared with the fasting lipid profile.* Lipids, 2010. **45**(12): p. 1127-38.

106. Schlitt, A., et al., *PLTP activity is a risk factor for subsequent cardiovascular events in CAD patients under statin therapy: the AtheroGene study.* J Lipid Res, 2009. **50**(4): p. 723-9.

107. Sediri, Y., et al., *Association of a DNA polymorphism of the apolipoprotein AI-CIII-AIV gene cluster with myocardial infarction in a Tunisian population.* Eur J Intern Med, 2011. **22**(4): p. 407-11.

108. Selden, M.A., et al., *Elevated alanine aminotransferase in current national football league players: correlation with cardiometabolic syndrome markers, obesity, and insulin resistance.* South Med J, 2009. **102**(10): p. 1003-6.

109. Shen, C., et al., *Association study of CRP gene and ischemic stroke in a Chinese Han population.* J Mol Neurosci, 2013. **49**(3): p. 559-66.

110. Shimbo, D., et al., *Endothelial dysfunction and the risk of hypertension: the multi-ethnic study of atherosclerosis.* Hypertension, 2010. **55**(5): p. 1210-6.

111. Shin, J.Y., H.R. Lee, and J.Y. Shim, *Significance of high-normal serum uric acid level as a risk factor for arterial stiffness in healthy Korean men.* Vasc Med, 2012. **17**(1): p. 37-43.

112. Shin, M.J. and R.M. Krauss, *Apolipoprotein CIII bound to apoB-containing lipoproteins is associated with small, dense LDL independent of plasma triglyceride levels in healthy men.* Atherosclerosis, 2010. **211**(1): p. 337-41.

113. Silbernagel, G., et al., *The relationships of cholesterol metabolism and plasma plant sterols with the severity of coronary artery disease.* J Lipid Res, 2009. **50**(2): p. 334-41.

114. Sossa, C., et al., *Insulin resistance status and four-year changes in other cardiometabolic risk factors in West-African adults: the Benin study.* Eur J Prev Cardiol, 2013. **20**(6): p. 1042-50.

115. Stamatakis, E. and M. Hamer, *The extent to which adiposity markers explain the association between sedentary behavior and cardiometabolic risk factors.* Obesity (Silver Spring), 2012. **20**(1): p. 229-32.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

116. Sumriddetchkajorn, K., et al., *Hypertension is statistically associated with higher body mass index but not with vitamin D level in a Thai population.* Eur J Clin Nutr, 2012. **66**(3): p. 405-7.

117. Talmud, P.J., et al., *Gene-centric association signals for lipids and apolipoproteins identified via the HumanCVD BeadChip.* Am J Hum Genet, 2009. **85**(5): p. 628-42.

118. Talmud, P.J., et al., *ANGPTL4 E40K and T266M: effects on plasma triglyceride and HDL levels, postprandial responses, and CHD risk.* Arterioscler Thromb Vasc Biol, 2008. **28**(12): p. 2319-25.

119. Tanaka, S., et al., *Serum levels of thiobarbituric acid-reactive substances are associated with risk of coronary heart disease.* J Atheroscler Thromb, 2011. **18**(7): p. 584-91.

120. Tani, S., et al., *Association of leukocyte subtype counts with coronary atherosclerotic regression following pravastatin treatment.* Am J Cardiol, 2009. **104**(4): p. 464-9.

121. Torres, F.S., et al., *Association between carotid intima-media thickness and retinal arteriolar and venular diameter in patients with hypertension: a cross-sectional study.* Atherosclerosis, 2013. **229**(1): p. 134-8.

122. Troughton, J.A., et al., *Paraoxonase activity and coronary heart disease risk in healthy middle-aged males: the PRIME study.* Atherosclerosis, 2008. **197**(2): p. 556-63.

123. Tsushima, M., et al., *Carotid intima media thickness and aortic calcification index closely relate to cerebro- and cardiovascular disorders in hemodialysis patients.* Int J Urol, 2008. **15**(1): p. 48-51; discussion 51-2.

124. Tu, J., et al., *Association of apolipoprotein A1 -75 G/A polymorphism with susceptibility to the development of acute lung injury after cardiopulmonary bypass surgery.* Lipids Health Dis, 2013. **12**: p. 172.

125. Vaisi-Raygani, A., et al., *Serum butyrylcholinesterase activity and phenotype associations with lipid profile in stroke patients.* Clin Biochem, 2009. **42**(3): p. 210-4.

126. Van Berendoncks, A.M., et al., *beta-blockers modify the prognostic value of adiponectin in chronic heart failure.* Int J Cardiol, 2011. **150**(3): p. 296-300.

127. Van Hemelrijck, M., et al., *Ability of a biomarker-based score to predict death from circulatory disease and cancer in NHANES III.* BMC Public Health, 2012. **12**: p. 895.

128. Vasan, R.S., et al., *Association of circulating cholesteryl ester transfer protein activity with incidence of cardiovascular disease in the community.* Circulation, 2009. **120**(24): p. 2414-20.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

129. Vidovic, B., et al., *Associations of oxidative stress status parameters with traditional cardiovascular disease risk factors in patients with schizophrenia.* Scand J Clin Lab Invest, 2014. **74**(3): p. 184-91.

130. Wagemakers, J.J., et al., *Consumption of red or processed meat does not predict risk factors for coronary heart disease; results from a cohort of British adults in 1989 and 1999.* Eur J Clin Nutr, 2009. **63**(3): p. 303-11.

131. Wakabayashi, I., *Inverse association between triglycerides-to-HDL-cholesterol ratio and alcohol drinking in middle-aged Japanese men.* J Stud Alcohol Drugs, 2012. **73**(6): p. 998-1004.

132. Wakabayashi, I. and K. Groschner, *Modification of the association between alcohol drinking and non-HDL cholesterol by gender.* Clin Chim Acta, 2009. **404**(2): p. 154-9.

133. Wang, Y., et al., *Diets high in total antioxidant capacity improve risk biomarkers of cardiovascular disease: a 9-month observational study among overweight/obese postmenopausal women.* Eur J Nutr, 2014. **53**(6): p. 1363-9.

134. Wilke, R.A., et al., *Quantification of the clinical modifiers impacting high-density lipoprotein cholesterol in the community: Personalized Medicine Research Project.* Prev Cardiol, 2010. **13**(2): p. 63-8.

135. Williams, P., et al., *Improvement in lipid profiles over 6 years of follow-up in adults with AIDS and immune reconstitution.* HIV Med, 2009. **10**(5): p. 290-301.

136. Windler, E., et al., *Association of plasma phytosterol concentrations with incident coronary heart disease Data from the CORA study, a case-control study of coronary artery disease in women.* Atherosclerosis, 2009. **203**(1): p. 284-90.

137. Worm, S.W., et al., *Elevated triglycerides and risk of myocardial infarction in HIV-positive persons.* AIDS, 2011. **25**(12): p. 1497-504.

138. Wu, J., et al., *Non-high-density lipoprotein cholesterol on the risks of stroke: a result from the Kailuan study.* PLoS One, 2013. **8**(9): p. e74634.

139. Wu, J., et al., *Association between non-high-density-lipoprotein-cholesterol levels and the prevalence of asymptomatic intracranial arterial stenosis.* PLoS One, 2013. **8**(5): p. e65229.

140. Yildiz, A., et al., *Association of paraoxonase activity and coronary blood flow.* Atherosclerosis, 2008. **197**(1): p. 257-63.

141. Yong, K., et al., *Interleukin-12 is associated with arterial stiffness in healthy individuals.* Am J Hypertens, 2013. **26**(2): p. 159-62.

142. Zamanian, R.T., et al., *Insulin resistance in pulmonary arterial hypertension.* Eur Respir J, 2009. **33**(2): p. 318-24.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

143. Zambon, A., et al., *Lipoprotein remnants and dense LDL are associated with features of unstable carotid plaque: a flag for non-HDL-C.* Atherosclerosis, 2013. **230**(1): p. 106-9.

144. Zhao, J., et al., *Association of thromboxane A2 receptor gene polymorphisms with cerebral infarction in a Chinese population.* Neurol Sci, 2013. **34**(10): p. 1791-6.

145. Zhu, C., et al., *Association of arterial stiffness with serum bilirubin levels in established coronary artery disease.* Intern Med, 2012. **51**(16): p. 2083-9.

E3. Association of CVD with factors other than HDL-C

1. Burchardt, P., et al., *Association between insulin like growth factor-1 and lipoprotein metabolism in stable angina patients on statin therapy: a pilot study.* Kardiol Pol, 2012. **70**(10): p. 1017-22.

2. Ito, K., et al., *Increased burden of cardiovascular disease in carriers of APOL1 genetic variants.* Circ Res, 2014. **114**(5): p. 845-50.

3. McNaughton, S.A., G.D. Mishra, and E.J. Brunner, *Food patterns associated with blood lipids are predictive of coronary heart disease: the Whitehall II study.* Br J Nutr, 2009. **102**(4): p. 619-24.

4. Navar-Boggan, A.M., et al., *Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease.* Circulation, 2015. **131**(5): p. 451-8.

5. Nishimukai, M., et al., *Serum choline plasmalogens-those with oleic acid in sn-2-are biomarkers for coronary artery disease.* Clin Chim Acta, 2014. **437**: p. 147-54.

6. Virani, S.S., et al., *Is high-intensity statin therapy associated with lower statin adherence compared with low- to moderate-intensity statin therapy? Implications of the 2013 American College of Cardiology/American Heart Association Cholesterol Management Guidelines.* Clin Cardiol, 2014. **37**(11): p. 653-9.

7. Zheng, T.P., et al., *Increased plasma DPP4 activities predict new-onset atherosclerosis in association with its proinflammatory effects in Chinese over a four year period: A prospective study.* Atherosclerosis, 2014. **235**(2): p. 619-24.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E4. Metabolic syndrome as the endpoint or the determinant

1. Arbel, Y., et al., *Relation of metabolic syndrome with long-term mortality in acute and stable coronary disease.* Am J Cardiol, 2015. **115**(3): p. 283-7.

2. Bachmayer, C., et al., *Adipokines and endothelial dysfunction in obesity WHO degrees III.* Microvasc Res, 2013. **89**: p. 129-33.

3. Boggio, A., et al., *Is thyroid-stimulating hormone within the normal reference range a risk factor for atherosclerosis in women?* Intern Emerg Med, 2014. **9**(1): p. 51-7.

4. Cuspidi, C., et al., *Metabolic syndrome and multiple organ damage in essential hypertension.* Blood Press, 2008. **17**(4): p. 195-203.

5. Ezzaher, A., et al., *Metabolic syndrome in Tunisian bipolar I patients.* Afr Health Sci, 2011. **11**(3): p. 414-20.

6. Graner, M., et al., *Electrocardiographic changes associated with insulin resistance.* Nutr Metab Cardiovasc Dis, 2014. **24**(3): p. 315-20.

7. Kahl, K.G., et al., *Prevalence of the metabolic syndrome in men and women with alcohol dependence: results from a cross-sectional study during behavioural treatment in a controlled environment.* Addiction, 2010. **105**(11): p. 1921-7.

8. Khader, Y.S., et al., *The association between metabolic syndrome and coronary artery disease in Jordan.* Chronic Illn, 2009. **5**(4): p. 235-42.

9. Kim, S.M., et al., *The effects of hormone therapy on metabolic risk factors in postmenopausal Korean women.* Climacteric, 2011. **14**(1): p. 66-74.

10. Kul, S., et al., *Metabolic syndrome and long-term cardiovascular outcomes in NSTEMI with unstable angina.* Nutr Metab Cardiovasc Dis, 2014. **24**(2): p. 176-82.

11. Kurt, M., et al., *The relationship between atrial electromechanical delay and P-wave dispersion with the presence and severity of metabolic syndrome.* Turk Kardiyol Dern Ars, 2012. **40**(8): p. 663-70.

12. Kwon, K.M., et al., *Inverse association between total bilirubin and metabolic syndrome in rural korean women.* J Womens Health (Larchmt), 2011. **20**(6): p. 963-9.

13. Lee, K., Y.M. Song, and J. Sung, *Genetic and environmental associations between C-reactive protein and components of the metabolic syndrome.* Metab Syndr Relat Disord, 2013. **11**(2): p. 136-42.

14. Lee, S.W., et al., *Association between menopausal symptoms and metabolic syndrome in postmenopausal women.* Arch Gynecol Obstet, 2012. **285**(2): p. 541-8.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

15. Lejskova, M., et al., *Natural postmenopause is associated with an increase in combined cardiovascular risk factors.* Physiol Res, 2012. **61**(6): p. 587-96.

16. Liu, L., et al., *Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan.* Am J Cardiol, 2014. **113**(1): p. 84-9.

17. Maciel, G.A., et al., *Association of glucocorticoid receptor polymorphisms with clinical and metabolic profiles in polycystic ovary syndrome.* Clinics (Sao Paulo), 2014. **69**(3): p. 179-84.

18. Margari, F., et al., *Metabolic syndrome: differences between psychiatric and internal medicine patients.* Int J Psychiatry Med, 2013. **45**(3): p. 203-26.

19. Martin Lde, S., et al., *Metabolic syndrome: a major risk factor for atherosclerosis in HIV-infected patients (SHIVA study).* Presse Med, 2008. **37**(4 Pt 1): p. 579-84.

20. Matsushita, K., et al., *Further inflammatory information on metabolic syndrome by adiponectin evaluation.* Int J Cardiol, 2008. **124**(3): p. 339-44.

21. Mebazaa, A., et al., *Metabolic syndrome in Tunisian psoriatic patients: prevalence and determinants.* J Eur Acad Dermatol Venereol, 2011. **25**(6): p. 705-9.

22. Mittal, G., et al., *Effect of angiotensin converting enzyme gene I/D polymorphism in patients with metabolic syndrome in North Indian population.* Chin Med J (Engl), 2011. **124**(1): p. 45-8.

23. Mommersteeg, P.M., et al., *Type D personality and metabolic syndrome in a 7-year prospective occupational cohort.* J Psychosom Res, 2011. **71**(5): p. 357-63.

24. Nahas, E.A., et al., *The 60- and 70-kDa heat-shock proteins and their correlation with cardiovascular risk factors in postmenopausal women with metabolic syndrome.* Cell Stress Chaperones, 2014. **19**(4): p. 559-68.

25. Orluwene, C.G. and M.O. Mommoh, *Plasma total homocysteine, high-sensitivity C-reactive protein and thyroid function in metabolic syndrome patients.* Niger Postgrad Med J, 2013. **20**(4): p. 286-90.

26. Papadakis, J.A., et al., *High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNFalpha treatment: correlation with disease activity.* Clin Exp Rheumatol, 2009. **27**(2): p. 292-8.

27. Patel, S.P., et al., *Association of metabolic syndrome and periodontal disease in an Indian population.* J Int Acad Periodontol, 2014. **16**(4): p. 98-102.

28. Rabkin, S.W., *The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis.* Metab Syndr Relat Disord, 2014. **12**(1): p. 31-42.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

29. Rodilla, E., et al., *Association between serum uric acid, metabolic syndrome and microalbuminuria in previously untreated essential hypertensive patients.* Med Clin (Barc), 2009. **132**(1): p. 1-6.

30. Rouch, I., et al., *Metabolic syndrome is associated with poor memory and executive performance in elderly community residents: the PROOF study.* Am J Geriatr Psychiatry, 2014. **22**(11): p. 1096-104.

31. Song, S., et al., *Three distinct clustering patterns in metabolic syndrome abnormalities are differentially associated with dietary factors in Korean adults.* Nutr Res, 2014. **34**(5): p. 383-90.

32. Steffen, L.M., et al., *A modified Mediterranean diet score is associated with a lower risk of incident metabolic syndrome over 25 years among young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study.* Br J Nutr, 2014. **112**(10): p. 1654-61.

33. Steffes, G.D., et al., *Prevalence of metabolic syndrome risk factors in high school and NCAA division I football players.* J Strength Cond Res, 2013. **27**(7): p. 1749-57.

34. Struja, T., et al., *The association between urinary phytoestrogen excretion and components of the metabolic syndrome in NHANES.* Eur J Nutr, 2014. **53**(6): p. 1371-81.

35. Sung, K.C., S.H. Wild, and C.D. Byrne, *Lipoprotein (a), metabolic syndrome and coronary calcium score in a large occupational cohort.* Nutr Metab Cardiovasc Dis, 2013. **23**(12): p. 1239-46.

36. Tanner, R.M., et al., *Association of the metabolic syndrome with atrial fibrillation among United States adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study).* Am J Cardiol, 2011. **108**(2): p. 227-32.

37. Vernarelli, J.A. and J.D. Lambert, *Tea consumption is inversely associated with weight status and other markers for metabolic syndrome in US adults.* Eur J Nutr, 2013. **52**(3): p. 1039-48.

38. Wang, Z.H., et al., *Expression of STAMP2 in monocytes associates with cardiovascular alterations.* Eur J Clin Invest, 2010. **40**(6): p. 490-6.

39. Yubero-Serrano, E.M., et al., *Oxidative stress is associated with the number of components of metabolic syndrome: LIPGENE study.* Exp Mol Med, 2013. **45**: p. e28.

40. Zocchi, L., et al., *Does the metabolic syndrome predict subclinical atherosclerotic damage in an asymptomatic population at intermediate cardiovascular risk?* Nutr Metab Cardiovasc Dis, 2013. **23**(9): p. 864-70.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E6. Association of HDL-C with other diseases/syndromes

1. Aksoy, Y., et al., *Carotid intima-media thickness: a new marker of patients with uterine leiomyoma.* Eur J Obstet Gynecol Reprod Biol, 2014. **175**: p. 54-7.

2. Belaj, K., et al., *Changes in lipid metabolism and extension of venous thromboembolism.* Ann Nutr Metab, 2014. **64**(2): p. 122-6.

3. Leite, A.C., V.M. Carneiro, and C. Guimaraes Mdo, *Effects of periodontal therapy on C-reactive protein and HDL in serum of subjects with periodontitis.* Rev Bras Cir Cardiovasc, 2014. **29**(1): p. 69-77.

4. Li, L., et al., *Oxidative LDL modification is increased in vascular dementia and is inversely associated with cognitive performance.* Free Radic Res, 2010. **44**(3): p. 241-8.

5. Magnussen, E.B., et al., *Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study.* Am J Obstet Gynecol, 2011. **204**(6): p. 526 e1-8.

6. Newson, R.S., et al., *Association between serum cholesterol and noncardiovascular mortality in older age.* J Am Geriatr Soc, 2011. **59**(10): p. 1779-85.

7. Rodriguez-Sanz, A., et al., *High-density lipoprotein: a novel marker for risk of in-hospital infection in acute ischemic stroke patients?* Cerebrovasc Dis, 2013. **35**(3): p. 291-7.

8. Shah, S.M., M. Ihsanullah, and A. Rasheed, *Association of lipoprotein-alpha with obesity in children and adolescents in district Swat.* J Ayub Med Coll Abbottabad, 2009. **21**(3): p. 145-8.

9. Sims, R., et al., *Patterns of relationships between cardiovascular disease risk factors and neurocognitive function in African Americans.* Ethn Dis, 2008. **18**(4): p. 471-6.

10. Watanabe, J., et al., *Proteomic profiling following immunoaffinity capture of high-density lipoprotein: association of acute-phase proteins and complement factors with proinflammatory high-density lipoprotein in rheumatoid arthritis.* Arthritis Rheum, 2012. **64**(6): p. 1828-37.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E8. Neonates, children, or adolescents

1. Aasvee, K., et al., *Aggregation of lipoprotein and inflammatory parameters in families with a history of premature myocardial infarction: the Tallinn myocardial infarction study.* Clin Chem Lab Med, 2008. **46**(11): p. 1602-8.

2. Gaillard, R., et al., *Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study.* Hypertension, 2014. **63**(4): p. 683-91.

3. Hatch, J., et al., *Non-invasive vascular imaging is associated with cardiovascular risk factors among adolescents with bipolar disorder.* Pediatr Cardiol, 2015. **36**(1): p. 158-64.

4. Hirschler, V., et al., *Association of lipoprotein-associated phospholipase A(2) activity with components of the metabolic syndrome in apparently healthy boys.* Cardiovasc Hematol Agents Med Chem, 2011. **9**(2): p. 78-83.

5. Hirschler, V., et al., *Impact of unhealthy lifestyle behaviors and obesity on cholesteryl ester transfer protein among adolescent males.* Arch Med Res, 2011. **42**(1): p. 53-9.

6. Kuwabara, M., et al., *Changes in cardiovascular risk factors over a 24-year follow-up period: a Japanese pediatric cohort study.* Hiroshima J Med Sci, 2012. **61**(4): p. 85-9.

7. Nelson, K.B., et al., *Headache and biomarkers predictive of vascular disease in a representative sample of US children.* Arch Pediatr Adolesc Med, 2010. **164**(4): p. 358-62.

8. Pan, Y. and C.A. Pratt, *Metabolic syndrome and its association with diet and physical activity in US adolescents.* J Am Diet Assoc, 2008. **108**(2): p. 276-86; discussion 286.

9. Patel, D.A., et al., *Serum alanine aminotransferase and its association with metabolic syndrome in children: the bogalusa heart study.* Metab Syndr Relat Disord, 2011. **9**(3): p. 211-6.

10. Schwandt, P., T. Bertsch, and G.M. Haas, *Anthropometric screening for silent cardiovascular risk factors in adolescents: The PEP Family Heart Study.* Atherosclerosis, 2010. **211**(2): p. 667-71.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E11. In vitro or animal studies

1. Linsel-Nitschke, P., et al., *Macrophage cholesterol efflux correlates with lipoprotein subclass distribution and risk of obstructive coronary artery disease in patients undergoing coronary angiography.* Lipids Health Dis, 2009. **8**: p. 14.

2. Shuhei, N., et al., *Effect of HDL composition and particle size on the resistance of HDL to the oxidation.* Lipids Health Dis, 2010. **9**: p. 104.

E12. Case studies

1. Negi, S.I., et al., *A novel mutation in the ABCA1 gene causing an atypical phenotype of Tangier disease.* J Clin Lipidol, 2013. **7**(1): p. 82-7.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

7.4 Appendix 4 Excluded studies from search 3

Literature retrieved using Search 3: To identify articles primarily relevant to the association of HDL-C to respiratory disease using the string: ((((((HDL-C OR high density lipoprotein) AND (respiratory disease AND association) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language].) AND Humans[Mesh])) NOT Diabetes) NOT low density

E1. Association of HDL-C with factors other than smoking, MRTPs, or nicotine replacement therapy (NRT)

1. Dubey, A., et al., *A study on association of leptin receptor gene polymorphism with obstructive sleep apnea syndrome in overweight and obese north Indian subjects.* Indian J Physiol Pharmacol, 2014. **58**(3): p. 222-8.
2. Reed, R.M., et al., *Elevated HDL cholesterol levels are associated with osteoporosis in lung transplant candidates with chronic obstructive pulmonary disease.* Respir Med, 2010. **104**(12): p. 1943-50.

E2. HDL-C not associated with risk of disease

1. Ahbab, S., et al., *Neck circumference, metabolic syndrome and obstructive sleep apnea syndrome; evaluation of possible linkage.* Med Sci Monit, 2013. **19**: p. 111-7.
2. Hao, J. and X.D. He, *Haplotype analysis of ApoAI gene and sepsis-associated acute lung injury.* Lipids Health Dis, 2014. **13**: p. 79.
3. Sanchez-de-la-Torre, M., et al., *Non-synonymous polymorphism in the neuropeptide S precursor gene and sleep apnea.* Sleep Breath, 2011. **15**(3): p. 403-8.
4. Trakada, G., et al., *Plasma visfatin levels in severe obstructive sleep apnea-hypopnea syndrome.* Sleep Breath, 2009. **13**(4): p. 349-55.

E4. Metabolic syndrome as the endpoint or the determinant

1. Mota, P.C., et al., *APAP impact on metabolic syndrome in obstructive sleep apnea patients.* Sleep Breath, 2011. **15**(4): p. 665-72.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

E8. Neonates, children, or adolescents

1. Marshall, N.S., et al., *Snoring is not associated with adverse effects on blood pressure, arterial structure or function in 8-year-old children: the Childhood Asthma Prevention Study (CAPS).* J Paediatr Child Health, 2011. **47**(8): p. 518-23.

2. Van Hoorenbeeck, K., et al., *Metabolic disregulation in obese adolescents with sleep-disordered breathing before and after weight loss.* Obesity (Silver Spring), 2013. **21**(7): p. 1446-50.

E12. Case studies

1. Relf, B.L., et al., *Genome-wide linkage of obstructive sleep apnoea and high-density lipoprotein cholesterol in a Filipino family: bivariate linkage analysis of obstructive sleep apnoea.* J Sleep Res, 2010. **19**(2): p. 349-57.

Confidentiality Statement

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.