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Insulin and Risk of Cardiovascular Disease
A Meta-Analysis

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Background—Our purposes were to estimate the strength of the longitudinal relationship between hyperinsulinemia and cardiovascular diseases (CVD) from the available literature and to identify study characteristics that modify this relationship.

Methods and Results—Articles were identified by means of a MEDLINE and Embase search and citation tracking. Eligible studies were prospective population-based cohort studies and nested case-control studies on the relationship between, on the one hand, fasting or nonfasting insulin levels and, on the other hand, myocardial infarction, death from coronary heart disease, and/or ECG abnormalities. Data were extracted pertaining to insulin measurements, type of outcome studied, adjustment for confounding, sex, mean age of the study population, follow-up period, insulin assay, and ethnic background (white or nonwhite). Associations of insulin and CVD were reexpressed in a uniform manner, an estimate of relative risk (RR) and 95% CI, to be used in meta–regression analyses. Twelve of 17 potentially eligible articles provided sufficient information. Overall, a weak positive association was found. The meta-analysis resulted in an estimated summary RR (95% CI) of 1.18 (1.08 to 1.29) for differences in insulin level, equivalent to the difference between the 75th and the 25th percentiles of the general population in the Netherlands. Ethnic background and type of insulin assay modified the relationship between insulin and CVD with borderline significance.

Conclusions—Hyperinsulinemia is a weak risk indicator for the occurrence of CVD. The relationship between hyperinsulinemia and CVD was modified by ethnic background and by the type of insulin assay involved. (***Circulation.*** **1998;97:996–1001.**)

Key Words: insulin ■ cardiovascular diseases ■ follow-up studies ■ meta-analysis ■ epidemiology

The effect of hyperinsulinemia on the occurrence of cardiovascular disease (CVD) has been studied in various large prospective studies but, as yet, no unequivocal relationship has been established.[1,2] It is known that hyperinsulinemia precedes type II diabetes and that it is associated with an adverse cardiovascular risk profile. Type II diabetes carries a strongly increased risk for CVD, but the role of hyperinsulinemia itself in this process is not clear.[3] Recent articles[4–6] suggest that hyperinsulinemia reflects a compensatory mechanism of decreased insulin sensitivity of the peripheral tissues to insulin. This "insulin resistance" might be essential in the pathogenesis of CVD and of type II diabetes.[7] At the moment, ongoing epidemiological studies investigating this mechanism are directed toward measuring specific levels of insulin and insulin resistance.[8,9] Nevertheless, sources of the heterogeneity that could explain earlier conflicting results remain obscure.[10] Previous reviews on this issue[1–5] have been narrative in nature. Therefore, we decided to perform a meta-analysis to estimate the strength of the longitudinal relationship between hyperinsulinemia and CVD and to identify study characteristics that modify this relationship.

Methods

Eligible Articles

Articles were identified by means of an Index Medicus (MEDLINE) and Embase search and by citation tracking covering the period 1966 to 1996. Key words were insulin, prospective, cohort, follow-up, cardiovascular, myocardial infarction, and electrocardiography. Eligible for inclusion were, on the one hand, prospective population-based cohort studies and nested case-control studies on insulin levels and, on the other hand, myocardial infarction, death from coronary heart disease, and/or ECG abnormalities. Data were extracted pertaining to fasting and nonfasting insulin levels, type of outcome studied (myocardial infarction, death from coronary heart disease, ECG abnormalities), confounders for which adjustment was made, sex, mean age of the study population, follow-up period, type of insulin assay involved, and ethnic background (white or nonwhite). If researchers presented different follow-up periods on the same study population, the study with the follow-up period closest to the mean of the other study populations in the meta-analysis was selected. Articles had to provide enough information to estimate a relative risk (RR) and a 95% CI or an approximation, such as an odds ratio. We abstracted the estimated RR, adjusted for the highest number of potentially confounding variables, from each of the original articles.

Standardization of Study–Specific Associations

The objectives of this meta-analysis were to obtain a summary estimate of the effect of hyperinsulinemia on CVD and to explore sources of heterogeneity among the RRs of the various studies. Analyses were performed separately for fasting and nonfasting insulin levels. Most studies provided fasting as well as nonfasting insulin levels, but only one association per study population could be used per analysis. This stratified analysis therefore prevented arbitrary choices from being made but made it possible to investigate the differences in RRs for fasting and nonfasting insulin levels. We obtained the summary estimate across the different study populations by first estimating a coefficient (b) that represented the relationship between insulin and CVD per study and subsequently estimating a weighted average of the coefficients. The weight of each study was calculated inversely to the variance estimate of the coefficient after reexpression of the SE in a uniform manner.[11] For cohort and nested case-control studies, the b represents the coefficient for the effect of one standard unit difference (to be specified) in insulin level in a Cox proportional hazards, logistic regression, or Poisson regression model.[12] The reexpressed RR of cardiovascular disease per specified uniform difference in insulin level is therefore exp(b), assuming that the RR is constant during follow-up and the absolute risk is small. In the same manner, the 95% CI can be calculated as exp(b±1.96 SE). For studies that did not directly supply data that allowed the calculation of b and its SE, the computation methods described by Greenland were used.[11] This calculation of the RRs (95% CI) shows a relative risk for a difference of 50 pmol/L (fasting insulin levels) or 250 pmol/L (nonfasting insulin levels). This approximates the difference between the 75th and the 25th percentiles in the 50- to 74-year-old general population in the Netherlands[13] for fasting and nonfasting insulin levels, respectively. If a study provided an RR without sufficient specification of the difference in insulin levels involved, tables and figures from the same article were used to estimate the difference in insulin levels at issue. Articles from the Kuopio study[14] and the Busselton study[15] did not provide enough information in tables and figures to identify the difference in insulin level for which the RRs were calculated. Therefore, data on insulin distribution in a Dutch general population was used to estimate the difference in insulin levels that the RR refers to in the Kuopio study. We postulated that the distributions of the two populations were similar, because mean insulin levels of the Dutch population[13] and the Kuopio study[14] were very similar. In the same way, data from the Helsinki study[16] were used to estimate the difference in insulin levels for the RR of the Busselton study.[15] The latter studies had in common that they measured insulin levels 1 hour after an oral glucose tolerance test. Sensitivity analyses were performed to evaluate the influence of these estimations on the final conclusions.[17]

Sources of Heterogeneity and Summary Estimates

Univariate and multivariate meta–regression analyses were used to identify study characteristics that could explain differences in the relationship between insulin and CVD.[11,18] With this approach, the logarithm of the study RR is regressed on study characteristics of interest. Fixed-effect linear regression models were fitted by weighted least squares.[11] The fit of the weighted regression model was evaluated by comparing the residual sum of squares to a χ^2 distribution.[11,19] A small probability value indicates a poor fit. The importance of various study characteristics was evaluated according to the size of the b value as well as its CI. Subsequently, summary estimates for the effect of hyperinsulinemia on CVD were provided, stratified according to the study characteristics that significantly modified the relationship. The importance of study characteristics identified by meta–regression analyses was confirmed by two different meta-analytic techniques: first, heterogeneity tests of pooled studies, of which small values of P indicate differences in the RRs (95% CI) of these studies,[11] and second, summary RRs (95% CI) of pooled studies, calculated according to fixed- as well as random-effects models.[20,21] Summary RRs (95% CI) calculated by fixed-effects models imply that differences in the RRs (95% CI) of pooled studies are due to sampling error.

Summary RRs (95% CI) calculated according to random-effects models make allowance for unidentified sources of heterogeneity beyond sampling error.[21] This incorporation of possible unidentified sources of heterogeneity in the random-effects models results, in general, in a greater contribution of smaller studies to the overall mean in the random-effects models than in the fixed-effects models. Differences between summary RRs (95% CI) calculated according to both models indicate unidentified sources of heterogeneity, in which case the RR (95% CI) of the random-effects model is the more appropriate. Otherwise, only RRs (95% CI) of the fixed-effects model are presented.[20,21] Study characteristics that were consecutively included in meta-regressions as possible sources of heterogeneity were the type of outcome studied (myocardial infarction and death from coronary heart disease and/or ECG abnormalities), adjustment for confounding (both the number of confounding variables and the presence or absence of control for a specific confounder), sex (male versus female or mixed population), mean age of the study population, length of follow-up period, insulin assay (specific insulin assay versus potential cross-reactivity with proinsulin-like molecules), and ethnic background (white versus nonwhite). Analyses were performed with the SPSS-PC software package, version 5.0.

Results

Twenty-two potentially eligible articles with data on insulin levels and CVD were identified.[14–16,22–40] Twelve articles describing 17 different studies were included in the meta–regression analyses and are listed in Table 1.[14,15,22–28,30,34,39] The coefficient, corresponding SE, and unit increment (specified difference in insulin level) derived from the original articles, before reexpression, are shown. Subsequently, RRs and 95% CIs are presented, after reexpression for a difference of 50 pmol/L fasting or 250 pmol/L nonfasting insulin. The Busselton,[15] Helsinki,[16,23] and British Regional Heart[27] studies provided data on different follow-up periods of the same study populations. One study per population was chosen, the closest to the mean follow-up period of the remaining studies. Sensitivity analyses revealed that using a study on any of the other reported follow-up periods had no substantial influence on the final conclusions[17] (data not shown). Eleven articles did not provide sufficient quantitative information for this meta-analysis. Two studies[30,34] could be included after additional details were provided by direct correspondence and are listed in Table 1. Five articles described study populations that had already been included,[35–38,40] and 4 other articles are listed in Table 2.[29,31–33] Of these 4 articles, 1 found a negative association between hyperinsulinemia and CVD,[32] and 3 did not find an association.[29,31,33]

Overall, this meta-analysis showed weak positive associations between insulin levels and CVD. An increase of 50 pmol/L fasting insulin resulted in a summary RR (95% CI) of 1.18 (1.08 to 1.29) before stratification (Table 3). However, the meta-analyses revealed heterogeneity across studies of nonfasting insulin and CVD (probability value of heterogeneity test, P=.007, Table 3). The heterogeneity might be explained by a difference between studies involving white and nonwhite populations. Separate summary RRs were 1.04 (0.93 to 1.16) for studies of nonwhite populations and 1.42 (1.23 to 1.65) for studies of white populations, respectively. Unfortunately, it was not possible to identify the study characteristic responsible for this heterogeneity, because ethnic background, mean age of study population, and the type of outcome studied were highly correlated within these studies.

TABLE 1.   Summary of Results of Prospective Studies Included in Meta–Regression Analyses of Insulin and Cardiovascular Disease

Study (Reference)	Time (h) Insulin After OGTT	Follow-up Period, y	Outcome	No. of Patients	Original Coefficient (SE)*			RR (95% CI) After Reexpression†
					Increment	Coefficient (b)	SE	
Studies in whites								
Helsinki study[23]‡	· · ·	9.5	MD	63	U20/L80	0.216	0.138	1.35 (0.93-1.97)
Paris study[24]§	· · ·	10	D	126	U20/L80	0.604	0.308	1.58 (1.00-2.49)
Kuopio study[14]‡	· · ·	3.5	MD	74	U20/L80	0.182	0.311	1.08 (0.83-1.40)
Quebec C study[28]‡‖	· · ·	5	MDE	91	1 SD	0.470	0.188	2.31 (1.20-4.46)
Edinburgh study[30]‡¶	· · ·	12	MD	11	· · ·	· · ·	· · ·	1.18 (0.92-1.51)
Danish study[39]§	· · ·	17	MD	123	1 mU/L	0.029	0.010	1.27 (1.08-1.49)
MRFIT study[34]‡‖¶	· · ·	7-10	MD	208	μU/mL	−0.12	0.179	1.01 (0.35-1.19)
Busselton study[15]	1	6	MD	114	U20/L80	0.513	0.199	1.41 (1.08-1.83)
Helsinki study[23]‡	2	9.5	MD	63	U20/L80	0.352	0.119	1.80 (1.22-2.65)
Paris study[25]§	2	15	D	174	U20/L80	0.438	0.169	1.30 (1.06-1.59)
British RH study[27]§	Nonfasting	11.5	MD	520	U10/L90	0.470	0.188	5.31 (1.43-19.7)
Studies in nonwhites								
Nauru study (female)[22]‡	· · ·	5	E	13	1 μU/mL	0.009	0.032	1.09 (0.64-1.84)
Nauru study (male)[22]‡	· · ·	5	E	6	1 μU/mL	0.030	0.022	1.27 (0.88-1.83)
Pima indian study[26]§	· · ·	6.7	E	16	U10/L10	0.833	0.452	1.15 (0.99-1.34)
Nauru study (female)[22]‡	2	5	E	14	1 μU/mL	0	0.003	1.00 (0.76-1.31)
Nauru study (male)[22]‡	2	5	E	6	1 μU/mL	−0.002	0.006	0.92 (0.53-1.59)
Pima indian study[26]§	2	6.7	E	16	U10/L10	0.419	0.511	1.05 (0.93-1.19)

OGTT indicates oral glucose tolerance test; M, myocardial infarction; D, death from coronary heart disease; and E, ECG abnormalities.

*Coefficient per increment (specified difference in insulin level) derived from the original article, adjusted by confounding variables mentioned in Table 4, but before reexpression, eg, a coefficient of 0.51 per U20/L80 is a coefficient of 0.51 for subjects with the highest 20% vs the lowest 80% of insulin levels.

†Relative risk (RR) and 95% CI after reexpression for a difference of 50 pmol/L fasting insulin or 250 pmol/L nonfasting insulin.

‡Logistic regression analysis.

§Cox regression analysis.

‖Nested case-control studies.

¶RR (95% CI) obtained by direct correspondence with the authors.

All studies of nonwhite populations had younger subjects and used only ECG abnormalities as outcome, in contrast to studies of white populations, which had older subjects and used clinical myocardial infarction or death from coronary heart disease as outcome (exception: see Reference 28). Another source of heterogeneity across studies, identified with meta–regression analyses, was the type of insulin assay involved. Although the probability value of the heterogeneity tests ($P=.09$, fasting studies in whites; $P=.11$, nonfasting studies in whites; Table 3) does not confirm strongly that this study

TABLE 2.   Summary of Results of Prospective Studies Not Included in Meta–Regression Analyses of Insulin and Cardiovascular Disease

Study (Reference)	Time (h) Insulin After OGTT	Follow-up Period, y	Outcome	No. of Patients	Original Coefficient (SE)*			Original Mean (SD)		
					Increment	Coefficient (b)	SE	Cases	Noncases	Units
Studies in whites										
Study of men born in 1913[29]‡	· · ·	8	MD	66				14.6 (9.0)	13.0 (8.8)	mU/L
San Luis Valley study[31]†	· · ·	4	M	72						
Caerphilly study[33]‡‖	· · ·	5	MD	113	1 SD	0.039	0.109	6.53 (6.7)	5.69 (5.9)	mU/L
Rancho Bernardo study[32]§	2	5	D	22	1 SD	−0.357	0.210	39.7	59.4	μU/mL

Abbreviations as in Table 1.

*Original coefficient (SE) as provided in the article, adjusted by confounding variables mentioned in Table 4. Reexpression of the association is not possible because the increment (specified difference in insulin level, eg, 1 SD) was expressed on a logarithmic scale.

†In the San Luis Valley Diabetes Study, no association was found (abstract).

‡Logistic regression.

§Cox regression analysis.

‖Nested case-control study.

TABLE 3. Meta-Analysis of Relationship Between Insulin and Cardiovascular Disease

Studies	No.	Fixed-Effects Model RR (95% CI)	Random-Effects Model RR (95% CI)*	P Value of Heterogeneity Test
All fasting insulin studies	10	1.17 (1.09-1.26)	1.18 (1.08-1.29)	.27
Studies in nonwhites	3	1.16 (1.02-1.33)		.84
Studies in whites	7	1.18 (1.08-1.29)	1.21 (1.06-1.39)	.09
Nonspecific insulin assay	6	1.16 (1.06-1.27)		.24
Specific insulin assay	1	2.31 (1.20-4.46)		. . .
All nonfasting insulin studies	7	1.16 (1.06-1.27)	1.25 (1.03-1.51)	.007
Studies in nonwhites	3	1.04 (0.93-1.16)		.87
Studies in whites	4	1.42 (1.23-1.65)	1.43 (1.23-1.66)	.11
Nonspecific insulin assay	3	1.40 (1.21-1.62)		.34
Specific insulin assay	1	5.31 (1.43-19.7)		. . .

Summary relative risks (RRs) are provided for a difference of 50 pmol/L fasting insulin or 250 pmol/L nonfasting insulin.
*Random-effects model RRs (95% CI) are provided only in cases of differences from fixed-effects model RRs (95% CI).

characteristic induces heterogeneity, meta–regression analyses are generally regarded to be more sensitive in revealing sources of heterogeneity.[11] In the fasting and nonfasting studies, only one study involved a specific insulin assay, and they both had higher RRs. Again, however, interference with other study characteristics could not be excluded. One of the studies[27] measured nonfasting insulin without using an oral glucose tolerance test, and the other[28] had a nested case-control design. A study that involved a nonspecific insulin assay and nested case-control design had a population selection of middle-aged men with a high-risk profile.[34] Adjustment for confounding varied greatly across studies for both type and number for which adjustment was made, as is shown in Table 4. In general, most studies adjusted only for a limited number of confounders. More than nine studies adjusted for age, body mass index, smoking, blood pressure, glucose level, cholesterol, and triglycerides. In our meta-regression, neither the number of confounding variables for which adjustment was made, the presence or absence of control for one specific confounder, length of follow-up period, nor sex differences in the study populations modified the association between insulin and CVD.

Discussion

In contrast to previous narrative reviews,[1–5] this meta-analysis provides a quantitative estimate of the strength of the longitudinal relationship between insulin and CVD and systematically investigates which study characteristics could be responsible for the heterogeneity of this relationship. The overall relationship between insulin and CVD turned out to be weak, and ethnic background as well as type of insulin assay involved were identified as potentially important study characteristics. The strength of the relationship was therefore presented for the different categories of these characteristics. However, both ethnic background and type of insulin assay involved were correlated to other study characteristics, and this might also be a cause of the modification effect. Thus, definite conclusions cannot yet be made on the basis of this meta-analysis alone,[41] but it stresses the importance of further research on these issues. Another remarkable finding was the great variety across studies in the number and type of confounding variables for which

adjustment was made. Although the absolute number of confounders adjusted for in the individual studies does not appear to be a modifier of the relationship between insulin and CVD, more research into the role of individual confounders or intermediates is also clearly needed.[2] The ability of this meta-analysis to identify important study characteristics was limited by the fact that some investigators adjusted for a particular study characteristic of interest, whereas other investigators excluded the same study characteristic by design (eg, sex, glucose intolerance). In future, a more uniform approach would facilitate meta–regression analyses to identify sources of heterogeneity and thus contribute to insight into pathogenic mechanisms.

The question of whether insulin itself increases the risk for CVD, independent of insulin resistance, cannot be answered by this meta-analysis, because none of the included studies measured both insulin and insulin resistance. Cross-sectional results of the IRAS study, in which insulin levels and insulin resistance both were measured in ≈1400 subjects, did not show an independent association between insulin level and CVD.[9] A recent experimental study also found no evidence of a role of exogenous insulin in accelerating atherosclerosis.[42]

The importance of ethnic background for the pathogenic mechanism is suggested by studies showing a stronger longitudinal relationship in white than in nonwhite populations. In studies of nonwhite populations, however, the outcome (CVD) was assessed only by means of electrocardiography, and the mean age of the study population was generally lower. ECG abnormalities reflect ischemia or previous myocardial infarction, whether or not clinically manifest, but obviously they do not reflect sudden coronary heart death. Clinical myocardial infarction and coronary heart death, by definition, reflect CVD. Theoretically, it is possible that the pathophysiology involved might be slightly different between these two outcomes. Pooling individual patient data from different studies would probably not reveal the responsible determinant either, because in various studies the distribution of determinants is highly influenced by the study design, resulting in an unresolved correlation between determinants.[14,22–28,39] Ethnic background as a modifier is further supported by the previously mentioned IRAS study[9] and by a discrepancy between low

TABLE 4. Summary of Confounding Variables Adjusted for in Prospective Studies on Insulin and Cardiovascular Disease

Confounding Variables	Table 1 (Included in Meta–Regression Analyses)															Table 2 (Not Included)			
	Whites							Nonwhites								Whites			
Reference	23	24	14	28*	30†	39	36*	15	23	25	27	22	26	22	26	29	31	33*	32
Time (h) insulin after OGTT	...	...	...	...	...	...	...	1	2	2	n-f	...	...	2	2	...	...	...	2
Prevalent CVD											•							•	
Age	•		•	•				•		•	•	•	•	•		•		•	
Sex			•		•									•	•				
Body mass index	•			•		•			•	•	•		•				•	•	
Waist-to-hip ratio		•																	
Physical activity	•					•	•		•		•								
Smoking	•		•	•		•	•				•								•
Alcohol consumption				•		•					•								•
Forced expiratory volume											•								
Social class											•								
Blood pressure	•		•					•	•	•	•	•	•		•				
Antihypertensive therapy				•							•								•
Glucose	•				•	•		•	•	•	•		•		•	•			•
Cholesterol	•		•			•		•	•	•	•		•		•	•			
HDL cholesterol				•		•	•				•								•
LDL cholesterol				•			•												
Triglycerides	•			•		•	•	•	•		•		•		•	•		•	
Heart rate											•								
Uric acid												•		•					
Apolipoprotein B				•															
Family history CVD				•															

OGTT indicates oral glucose tolerance test; n-f, nonfasting; and CVD, cardiovascular disease.

*Nested case-control study.

†Information obtained by direct correspondence with the authors.

rates of CVD and high rates of non–insulin–dependent diabetes mellitus in Pima Indians.[43] In our study, the type of insulin assay involved turned out to be another potentially important modifier. In contrast to expectations, studies with a specific insulin assay[27,28] had a high RR, despite recent findings that showed the importance of proinsulin and split products in accelerating atherosclerosis.[44,45] Again, correlation with other study characteristics made it impossible to draw definite conclusions on this issue. In future research, however, detailed measurements of specific insulin, proinsulin, and insulin–like molecules with specific assays[44,45] are needed, as well as specific measurements of insulin resistance.

This meta-analysis is based on a limited number of articles, of which a substantial proportion provided insufficient information. A few articles provided means (and SDs) of cases and controls to show the relationship between insulin and CVD. Unfortunately, procedures to estimate RRs (with 95% CI) from means (and SDs) for these studies could not be performed, because insulin distributions are typically highly skewed.[11] Except for the MRFIT[34] and the Edinburgh study,[30] an attempt to gather additional information from these studies by direct correspondence with the authors provided no additional ways of calculating RRs. Another limitation was "presentation bias," ie, some articles provided more information on

statistically significant than on statistically nonsignificant associations. For example, although the relevant data were collected,[25] the "15-year follow-up" article of the Paris Prospective Study did not provide enough information on the nonsignificant association between fasting insulin and CVD to reexpress the RR (95% CI). A more general limitation in review of the literature is that it is prone to publication bias. We explicitly investigated this by plotting the number of cases versus effect magnitude, which resembled a funnel,[46] indicating the relative absence of publication bias (data not shown). Estimates with a small sample size were spread out over a wide range, and estimates with a large sample size were spread out over a smaller range; no discontinuity could be found. Publication bias might be limited for the above-mentioned topic, because in this area negative as well as positive results are generally considered to be clinically relevant.[7] In the meta-analysis, no assessment of the methodological quality of the studies was made, because this is highly arbitrary.[21,47,48]

The advantage of this meta-analysis is that it clearly identifies sources that could potentially modify the relationship between insulin and CVD. Moreover, it reveals issues that vary greatly between studies (eg, number and type of confounding or intermediate variables) or are in need of improvement (eg, correct presentation of significant as well as nonsignificant data). In

conclusion, both fasting and nonfasting hyperinsulinemia seem to be weak risk indicators for the occurrence of CVD. Sources that could potentially modify the relationship between insulin and CVD are ethnic background and type of insulin assay.

Acknowledgments

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