

## Estimated Coronary Heart Disease Attributable to Insulin Resistance in Populations With and Without Type 2 Diabetes Mellitus

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**Objective:** To estimate the annual number and costs of coronary heart disease (CHD) events in the United States attributable to insulin resistance among individuals with and without type 2 diabetes.

**Research Design and Methods:** Medline-indexed articles and government statistical reports were screened for data on the prevalence of insulin resistance, the relative risk of CHD by insulin resistance status, and number of CHD events per year among individuals with and without type 2 diabetes. These data were used to estimate the number of CHD events per year by insulin resistance and type 2 diabetes status, the proportion of CHD events attributable to insulin resistance, and the annual cost of these events.

**Results:** Of the 171,000 annual CHD events in the type 2 diabetes population, 164,000 (96%) occurred in those with insulin resistance, 80,000 of which were attributable to insulin resistance. Of the 929,000 annual CHD events in the non-type 2 diabetes population, 162,000 (17%) occurred in patients with insulin resistance, 58,000 of which were attributable to insulin resistance. Thus, insulin resistance is responsible for 46.8%, 6.2%, and 12.5% of the annual CHD events in the type 2 diabetes, non-type 2 diabetes, and total US population, respectively. The estimated annual total cost of these insulin resistance-attributable events was \$12.5 billion in the United States in 1999, of which \$6.6 billion were direct medical costs.

**Conclusion:** Preventing or modifying insulin resistance may reduce the morbidity, mortality, and costs associated with CHD.

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Type 2 diabetes has been consistently associated with increased risk and earlier onset of heart disease, loss of the cardiac gender advantage for females, and earlier mortality compared with that seen in the general population.<sup>1</sup> This increased risk appears to be independent of the

effect of the other cardiovascular risk factors including hypertension, dyslipidemia, and smoking.<sup>2-4</sup>

Attention has been drawn to the role of insulin as an etiologic factor in determining cardiovascular risk in individuals with and without type 2 diabetes. However, the relationship between insulin resistance or hyperinsulinemia and cardiovascular disease is complex.<sup>5,6</sup> Insulin resistance is defined as a submaximal response to glucose. In addition to its direct effects on atherosclerosis, insulin has been associated with a number of cardiovascular risk factors including dyslipidemia, central adiposity, hypertension, and the clustering of these factors.<sup>6</sup> This clustering, referred to as the insulin resistance syndrome, is strongly associated with the development of type 2 diabetes.<sup>5</sup>

There are limited data examining the impact of insulin resistance on coronary heart disease (CHD), primarily due to the complexity and difficulties of directly measuring insulin sensitivity. Large epi-

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demographic studies have evaluated hyperinsulinemia, both as a direct risk factor and as a surrogate marker for insulin resistance. Several of these studies reported a positive relationship between hyperinsulinemia and the development of CHD in the general population.<sup>7-15</sup> However, inconsistent results also have been reported, including the absence of a relationship<sup>16-20</sup> or an inverse relationship.<sup>21,22</sup> These conflicting findings may, in part, reflect differences in methodology and study populations. In addition, hyperinsulinemia is not an adequate surrogate marker of insulin resistance at all the stages of disease development. Type 2 diabetes patients in later stages of disease who are highly insulin resistant may have relative hypoinsulinemia as a result of beta-cell dysfunction.<sup>5</sup> More definitive studies, which have been designed to address this issue, are currently ongoing.

This analysis attempts to fill a gap in the available literature by estimating the annual number and costs of CHD events attributable to insulin resistance in the United States and may provide a new perspective for assessing the potential impact of an intervention for insulin resistance. While research has been performed to establish the validity and strength of the insulin resistance-CHD association,<sup>6,23</sup> to our knowledge this is the first report quantifying the attributable risk of CHD by insulin resistance status and its related economic impact.

... RESEARCH DESIGN AND METHODS ...

A literature search was conducted of Medline-indexed articles to cull data on the distribution of insulin resistance among those with and without type 2 diabetes, the association of insulin resistance with heart disease, and the number of CHD events per year expected in these 2 groups. Government statistical reports also were reviewed for this information as well as for data on the size of the US population. Estimates were developed from these data of the number of CHD events per year by insulin resistance and type 2 diabetes status, the proportion of these events attributable to insulin resistance, and the annual cost of these events.

“Without type 2 diabetes” specifically refers to individuals who have not been diagnosed with type 2 diabetes (it does not refer to individuals with type 1 diabetes). The working definition of insulin resistance was limited in our report to how it was defined in the available literature. In general, in the literature applied insulin resistance was defined as a clustering of risk factors for insulin resistance; however, the definition was not consistent across the literature sources. A simplified model was then developed using the data elements outlined in **Table 1**.

Several data points were estimated from the available published literature. Although Haffner et al reported that 92% of those with type 2 diabetes have insulin resistance, defined by intravenous glucose tolerance,<sup>27</sup> little was available regarding the prevalence of insulin resistance among those without type 2 diabetes. The conservative estimate of 12% was assigned based on the proportion of individuals without type 2 diabetes who had insulin resistance as determined by the co-occurrence of hypertension and dyslipidemia in the Atherosclerosis Risk in Communities (ARIC) cohort.<sup>28,29</sup> Indicators of hypertension include elevated systolic blood pressure, elevated diastolic blood pressure, or the use of pharmacotherapy for hypertension; dyslipidemia has been defined by elevated triglycerides and/or low high-density lipoprotein cholesterol. While this estimate may not be ideal, it does provide a conservative approximation, and it has been included in our sensitivity analyses. The relative risk (RR) of 3 was assigned as the estimate for the effect of type 2 diabetes on the development of CHD, as the literature reflected an RR range of 2 to 4.<sup>1,2,11,30</sup> The RR of CHD due to insulin resistance in individuals without type 2 diabetes (1.55) was calculated as the weighted average from several large epidemiologic studies in different populations.<sup>7-9,11,18,21,32-35</sup> All published

**Table 1.** Data Assumptions for Model Calculations

<ul style="list-style-type: none"> <li>■ 1998 US population<sup>24</sup></li> <li>■ The total number of annual coronary heart disease events (myocardial infarction and fatal coronary heart disease)<sup>25</sup></li> <li>■ The prevalence of type 2 diabetes in the US population<sup>26</sup></li> <li>■ The proportions of the type 2 diabetes population with and without insulin resistance<sup>27</sup></li> <li>■ The proportions of the non-type 2 diabetes population with and without insulin resistance<sup>28,29</sup></li> <li>■ The relative risk of coronary heart disease for individuals with type 2 diabetes versus those without type 2 diabetes<sup>1,2,11,30</sup></li> <li>■ The relative risk of coronary heart disease for individuals who have type 2 diabetes with insulin resistance versus those who have type 2 diabetes without insulin resistance<sup>31</sup></li> <li>■ The relative risk of coronary heart disease for non-type 2 diabetes populations with insulin resistance versus non-type 2 diabetes populations without insulin resistance<sup>7-9,11,18,21,32-35</sup></li> <li>■ The total annual estimated cost of coronary heart disease events, including direct and indirect costs<sup>25</sup></li> </ul>
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reports from prospective cohort studies, excluding the 2 nested case-control studies<sup>10,17</sup> that examined the risk of hyperinsulinemia for CHD, were included. The weighted average and 95% confidence intervals (95% CIs) were calculated based on the number of events in each study using a log-transformed ratio measure.

We derived the insulin resistance-attributable CHD event rates by using a simplified model. The proportions of the total annual CHD events by type 2 diabetes status were generated using the size of the type 2 diabetes and non-type 2 diabetes populations, the total annual CHD events, and the RR of CHD events for type 2 diabetes versus non-type 2 diabetes populations. The annual number of CHD events in the insulin resistance and non-insulin resistance type 2 diabetes and non-type 2 diabetes populations was derived from the size of the type 2 diabetes and non-type 2 diabetes populations, the annual CHD events in the type 2 diabetes and non-type 2 diabetes populations, the proportions of the type 2 diabetes and non-type 2 diabetes populations with and without insulin resistance, and the RR of CHD relative to insulin resistance status for the type 2 diabetes and non-type 2 diabetes populations.

The incidence of CHD events attributable to insulin resistance in the type 2 diabetes and non-type 2 diabetes populations was estimated by subtracting the incidence of CHD in each insulin resistance group from that of the corresponding non-insulin resistance group. These attributable risks were then multiplied by the number of people with insulin resistance in the corresponding type 2 diabetes and non-type 2 diabetes populations. This provided the number of CHD events attributable to insulin resistance in the type 2 diabetes and non-type 2 diabetes populations. These figures were summed to get the number of CHD events attributable to insulin resistance for the entire US population.

Finally, using estimates of total CHD costs,<sup>25</sup> the average cost per CHD event was calculated for each component of direct (hospital/nursing home, physician/other professionals, drugs, and home health/other medical durables) and indirect (lost productivity/morbidity and lost productivity/mortality) cost. Dividing these annual cost estimates by the total number of annual CHD events provided the estimated cost per CHD event, in total and by cost component. The estimated costs per event were then multiplied by the number of CHD events attributable to insulin resistance in each population to derive the total cost due to insulin resistance in each population. Costs were expressed in 1999 dollars.

It was assumed that the cost of a CHD event did not vary by insulin resistance or type 2 diabetes status. This assumption was necessary for insulin resistance, since no data were identified to support a differential in CHD costs by levels of insulin resistance or "severity." In addition, this assumption probably led to conservative cost estimates for those with type 2 diabetes, since the costs related to a CHD event are likely higher for those with type 2 diabetes than the average cost estimates indicate. However, detailed national cost estimates for CHD events by type 2 diabetes status were not identified, and the analysis was necessarily limited to using available data.

Sensitivity analyses were performed to test the robustness of the model when subjected to the uncertainty of the various estimates. Estimates tested include the RR for CHD by type 2 diabetes status, the RR for CHD by insulin resistance status for the type 2 diabetes and non-type 2 diabetes populations, and the proportion of those with insulin resistance in the non-type 2 diabetes population. The RR of type 2 diabetes status for the development of CHD in the total population was evaluated using lower and upper bounds of 2 and 4, respectively, based on the published range of findings.<sup>1,2,11,30</sup> For the non-type 2 diabetes population, the RR of insulin resistance for CHD estimates of 1.24 ( $1.55 \times [1 - 20\%]$ ) and 1.86 ( $1.55 \times [1 + 20\%]$ ) were substituted for the 1.55 average RR to evaluate the behavior of the model at the lower and upper bounds, respectively. Lower- and upper-bound estimates for the RR of insulin resistance in type 2 diabetes of 1.56 ( $1.95 \times [1 - 20\%]$ ) and 2.34 ( $1.95 \times [1 + 20\%]$ ), respectively, were also substituted in the model for the 1.95 RR estimate for the type 2 diabetes population. The sensitivity of the proportion of non-type 2 diabetes population with insulin resistance was tested using lower and upper bounds of 10%<sup>32</sup> and 25%,<sup>17,21,22</sup> respectively. Finally, multifactor sensitivity analyses were performed using extreme values from the above ranges.

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## ... RESULTS ...

The prevalence of insulin resistance was reported to be 92%<sup>27</sup> among those with type 2 diabetes and 12%<sup>28,29</sup> among the general non-type 2 diabetes population. There was a paucity of published data in the literature reflecting the risk of CHD relative to insulin resistance in type 2 diabetes patients, per-

haps due to its high prevalence in this group. However, one study<sup>31</sup> found that insulin resistance increases the risk of a CHD event almost 2-fold (RR = 1.95) in the type 2 diabetes population. Numerous literature sources<sup>7-9,11,18,21,32-35</sup> were available for the non-type 2 diabetes population, so an event-weighted average RR of 1.55 (95% CI = 0.6, 3.8) was calculated from these studies. **Table 2** provides the basic parameters of the model and results.

Of the 1.1 million annual CHD events in the United States, 84% are estimated to occur in individuals without type 2 diabetes. Of the 171,000 annual CHD events in the type 2 diabetes population, 96% occur among those with insulin resistance, while 17% of the 929,000 annual CHD events in the non-type 2 diabetes population occur among those with insulin resistance.

Further analysis using the derived attributable-risk data shows that 80,000 of the annual CHD events in those with type 2 diabetes and 58,000 of the annual CHD events in those without type 2 diabetes are attributable to insulin resistance. Thus, insulin resistance is responsible for 46.8%, 6.2%, and 12.5% of the annual CHD events in the type 2 diabetes, non-type 2 diabetes, and total US population,

respectively (**Figure**). The annual costs of US CHD events attributable to insulin resistance in 1999 were estimated at \$12.5 billion, of which \$6.6 billion were direct medical costs (**Table 3**).

**Sensitivity Analysis**

The robustness of the model was tested using uni-factor and multifactor sensitivity analysis, the results of which are outlined in **Table 4**. The baseline model results were regenerated using lower- and upper-bound estimates of the RR for the effect of type 2 diabetes on development of CHD. The upper- and lower-bound estimates provided a range of approximately \$3.5 billion in total costs, but did not impact the proportion of cases with insulin resistance in either group.

The model's sensitivity to the RR estimates for CHD relative to insulin resistance status for the type 2 diabetes and non-type 2 diabetes populations were then examined. In the type 2 diabetes population, the lower-bound estimate reduces the annual CHD attributable to insulin resistance from 46.8% to 34.0%, and the upper-bound estimate increases the estimate of insulin resistance-attributable CHD events to 55.2%. In the non-type 2 diabetes popu-

**Table 2.** Model for Coronary Heart Disease Events Attributable to Insulin Resistance

Population Diabetes Status		Parameters of the Model*				
		Proportion of Population with Insulin Resistance	RR for CHD by Insulin Resistance Status	Total Annual CHD Events	No. of CHD Events per Year	No. of CHD Events Attributable to Insulin Resistance
With type 2 diabetes	With insulin resistance	0.92 <sup>27</sup>	1.95 <sup>31</sup>	171,000	164,000	80,000
	Without insulin resistance	0.08 <sup>27</sup>			7000	
Without type 2 diabetes	With insulin resistance	0.12 <sup>28,29</sup>	1.55 <sup>7-9,11,18,21,32-35</sup>	929,000	162,000	58,000
	Without insulin resistance	0.88 <sup>28,29</sup>			767,000	

CHD = coronary heart disease; RR = relative risk.

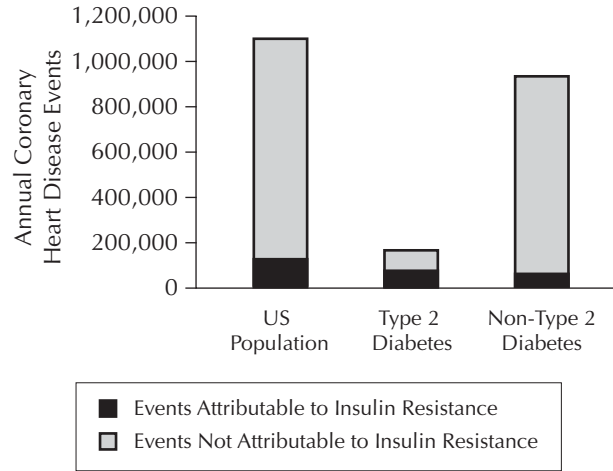
\*1998 US population = 270,029,000<sup>24</sup>; number of individuals with type 2 diabetes = 15,600,000<sup>26</sup>; total annual CHD events = 1,100,000<sup>25</sup>; total annual direct costs of CHD events = \$53 billion<sup>25</sup>; RR of CHD by type 2 diabetes status = 3.0.<sup>1,2,11,30</sup>

lation, the lower-bound estimate decreases the estimate of insulin resistance-attributable CHD events from 6.2% to 2.8%, while the upper-bound estimate increases it to 9.4%. The resultant insulin resistance attributable range was 7.6% to 16.5% of all CHD events.

Next, we examined the sensitivity of the model to changes in the estimated proportion of the non-type 2 diabetes population with insulin resistance. Lower and upper bounds of 10% and 25% (around the estimated 12% proportion of the non-type 2 diabetes population with insulin resistance) were substituted into the model. These adjustments indicated that the percentage of CHD events attributable to insulin resistance in the non-type 2 diabetes population ranged from 5.2% to 12.1%.

The impact of varying multiple parameters simultaneously also was addressed (Table 4). The combination of parameters (insulin resistance-attributable CHD risk in the non-type 2 diabetes population and the proportion of the non-type 2 diabetes population with insulin resistance) had a large impact on the percentage of CHD events attributable to insulin resistance in this group. The sensitivity analysis produced a range of values from

**Figure.** Annual Coronary Heart Disease Events Attributable to Insulin Resistance



2.3% to 17.7% for the proportion of insulin resistance-attributable CHD events in the non-type 2 diabetes population. Using these extreme estimates combined with estimates of the risk of CHD relative to insulin resistance in the type 2 diabetes population provided

**Table 3.** Coronary Heart Disease Costs Attributable to Insulin Resistance

Costs	Total Costs Attributable to Insulin Resistance (\$)			All CHD Events Attributable to Insulin Resistance
	Estimated Cost per Event	Type 2 Diabetes	Non-Type 2 Diabetes	
<b>Direct</b>				
Hospital/nursing home	37,000	2,950,287,500	2,129,139,773	5,079,427,273
Physician/other professionals	7000	558,162,500	402,810,227	960,972,727
Drugs	2910	232,036,125	167,453,966	399,490,091
Home health/other medical durables	1360	108,443,000	78,260,273	186,703,273
<i>Total direct costs</i>	<i>48,270</i>	<i>3,848,929,125</i>	<i>2,777,664,239</i>	<i>6,626,593,364</i>
<b>Indirect</b>				
Lost productivity/morbidity	6270	499,954,125	360,802,875	860,757,000
Lost productivity/mortality	36,180	2,884,902,750	2,081,953,432	4,966,856,182
<i>Total indirect costs</i>	<i>42,450</i>	<i>3,384,856,875</i>	<i>2,442,756,307</i>	<i>5,827,613,182</i>
<b>Total</b>	<b>90,720</b>	<b>7,233,786,000</b>	<b>5,220,420,546</b>	<b>12,454,206,546</b>

CHD = coronary heart disease.



the outlying values for this model. This estimate incorporates the variability in CHD RR estimates for the type 2 diabetes and non-type 2 diabetes populations, as well as that for the proportion of the non-type 2 diabetes population with insulin resistance. The resulting range of total annual US CHD costs attributable to insulin resistance is \$7.3 to \$23.5 billion.

... DISCUSSION ...

This analysis estimated the substantial impact of insulin resistance on CHD in the US population. Our model demonstrates that, even with conservative estimates, a large number of annual CHD events and their subsequent costs can be attributed to insulin resistance and that the prevention of insulin resistance may yield significant clinical and economic benefits.

Data from numerous sources were used to determine the population, events, RRs, and costs required for the model calculations, but our study was limited to the data available in the published literature. Therefore, the caveats of this approach must be borne in mind. Particular areas that deserve special consideration are discussed below.

It should be noted that our working definition of insulin resistance was limited to how it was defined in the available literature. Generally insulin resistance was defined in the literature as a clustering of risk factors for insulin resistance; however, the definition was not consistent across the literature sources. Thus, although this analysis used the best available information, it does rely on the varying definitions of insulin resistance used in the literature.

A limitation of this analysis is the paucity of published data in the literature reflecting the risk of CHD relative to insulin resistance in type 2 diabetes patients, since only 1 study<sup>31</sup> provided this informa-

**Table 4.** Sensitivity Analysis

Variable	Outcome Based on RR		
	Baseline Value	Lower Bound	Upper Bound
<b>RR for CHD relative to insulin resistance status</b>	<b>3.0</b>	<b>2.0</b>	<b>4.0</b>
CHD events (%) attributable to insulin resistance in individuals with type 2 diabetes	80,000 (46.8%)	56,000 (47.9%)	101,000 (46.5%)
CHD events (%) attributable to insulin resistance in individuals without type 2 diabetes	58,000 (6.2%)	61,000 (6.2%)	55,000 (6.2%)
<b>RR for CHD relative to insulin resistance status in individuals with type 2 diabetes</b>	<b>1.95</b>	<b>1.56</b>	<b>2.34</b>
CHD events (%) attributable to insulin resistance in individuals with type 2 diabetes	80,000 (46.8%)	58,000 (34.0%)	94,000 (55.2%)
<b>RR for CHD relative to insulin resistance status in individuals without type 2 diabetes</b>	<b>1.55</b>	<b>1.24</b>	<b>1.86</b>
CHD events (%) attributable to insulin resistance in individuals without type 2 diabetes	58,000 (6.2%)	26,000 (2.8%)	87,000 (9.4%)
<b>Simultaneous adjustment of RR of CHD individuals with and without type 2 diabetes</b>	<b>1.95/1.55</b>	<b>1.56/1.24</b>	<b>2.34/1.86</b>
CHD events (%) in both type 2 diabetes and non-type 2 diabetes populations	(12.5%)	(7.6%)	(16.5%)
<b>Proportion of non-type 2 diabetes population with insulin resistance</b>	<b>0.12</b>	<b>0.10</b>	<b>0.25</b>
CHD events (%) attributable to insulin resistance in individuals without type 2 diabetes	(6.2%)	(5.2%)	(12.1%)
<b>Simultaneous adjustment of proportion of non-type 2 diabetes population with insulin resistance and RR of CHD for insulin resistance</b>	<b>0.12/1.55</b>	<b>0.10/1.24</b>	<b>0.25/1.86</b>
CHD events (%) attributable to insulin resistance in individuals without type 2 diabetes	(6.2%)	(2.3%)	(17.7%)

CHD = coronary heart disease; RR = relative risk.

tion. Additional support for the present analysis would be gained with corroborating sources of data on the risk of CHD relative to insulin resistance in type 2 diabetes patients. However, to understand how variations in this estimate could affect the analysis, it was included in our sensitivity analyses.

One potential weakness of our approach is the estimation of the prevalence of insulin resistance in the general population. Hollenbeck et al reported that approximately 25% of non-type 2 diabetes patients have levels of insulin resistance, as assessed by the clamp technique, similar to those in patients with type 2 diabetes.<sup>36</sup> While the study was not based on a population sample, it highlights the variability of insulin action in healthy individuals. The epidemiologic studies of insulin and CHD were based on distribution cut-points of 10% to 25% as criteria for insulin resistance.<sup>7,9,11-14,16-18,32,34</sup> Although derived, these thresholds are consistent with the findings of Hollenbeck et al. We also relied on the ARIC study to estimate the proportion of the insulin resistance syndrome in the non-type 2 diabetes population. Data from 2 studies<sup>28,29</sup> indicate that approximately 12% of the ARIC cohort without type 2 diabetes had hypertension and dyslipidemia, suggesting the presence of insulin resistance syndrome. As these studies were performed in a range of different populations, the conservative estimate of 12% was chosen for inclusion in the model and the sensitivity analysis used 10% and 25% as the lower- and upper-bound estimates, respectively.

Another area of consideration is the estimation of risk of CHD associated with insulin resistance. Currently, there is no direct evidence linking insulin resistance to cardiovascular outcomes, because the large epidemiologic studies to date have relied on markers for insulin resistance. These studies used different definitions of insulin resistance and different methods of assessing insulin resistance in examining the RR of insulin resistance for CHD and were performed in various age groups and populations.

The RR of developing CHD in those with or without insulin resistance in the non-type 2 diabetes population was calculated as an event-weighted average of the epidemiologic studies of hyperinsulinemia and CHD.<sup>7-9,11,18,21,32-35</sup> Although the 95% CI for this estimate (0.6, 3.8) does not approach statistical significance, Ruige et al have shown insulin to be a weak but significant independent predictor of CHD using meta-analysis,<sup>37</sup> which provides support that this estimate (1.55) appropriately reflects the RR in the non-type 2 diabetes population. It is important to note that this estimate is based on a

marker of insulin resistance, not on a direct measure. Fasting insulin levels, as a marker, have been shown to correlate ( $r^2 \sim 0.45$ ) with direct measurements of insulin resistance.<sup>38</sup> The current results are based on the estimate of the RR for hyperinsulinemia, and the relationship between CHD and insulin resistance would be expected by many to be stronger if a direct measurement of insulin resistance were available. In addition, the estimate includes studies in the elderly, results of which probably reflect a conservative survival bias. More importantly, the estimated RR reflects data adjusted for lipids, blood pressure, and other factors known or likely to be part of the causal pathway for insulin resistance. The impact of these adjustments on the study results, if any, would be to underestimate the real effect.

Finally, consideration should be given to estimating the CHD risk among those with insulin resistance in the type 2 diabetes population. To our knowledge, only 1 study has attempted to address this issue using clustering of insulin resistance syndrome factors. In the Diabetes Intervention Study, the approach was to focus on the insulin resistance syndrome rather than only on insulin levels.<sup>31</sup> The study found that those with the clustering of hyperinsulinemia, hypertension, and dyslipidemia had a RR of developing CHD of 1.95,<sup>31</sup> although the difference did not achieve statistical significance. A limitation of this study is the definition of insulin resistance, which included hyperinsulinemia, hypertension, and dyslipidemia. This definition resulted in a prevalence of insulin resistance in individuals with type 2 diabetes of approximately 50%, much lower than previous estimates from metabolic studies.<sup>27</sup> Regardless, these results are supported by results from the Bedford study<sup>39</sup> and the Pima Indians Study.<sup>18</sup> These 2 studies suggest that disease progression, through eventual beta-cell dysfunction and relative hypoinsulinemia, is related to CHD. In addition, insulin resistance is known to be a fundamental defect in patients with type 2 diabetes.<sup>5</sup> This risk is currently under investigation in studies such as the Insulin Resistance and Atherosclerosis Study.

Relative risk estimates of CHD used in this study were not annualized; rather, they were based on the number of years of study follow-up. The CHD events and subsequent cost estimates used in this modeling analysis were based on annual figures; thus, it is necessary to assume that the CHD incidence rates in the insulin resistance and non-insulin resistance proportions of the type 2 diabetes and non-type 2 diabetes populations remain relatively constant over

time. It is not necessary to assume that these rates are static. Instead, it was assumed that if they change, the changes must occur at similar rates. With this assumption, annualized RR estimates would be similar to those based on data from a number of years of follow-up.

... CONCLUSIONS ...

We estimated that 12.5% of annual CHD events and \$12.5 billion of the total annual cost of CHD events in the United States are attributable to insulin resistance. The majority of this burden is among individuals with type 2 diabetes. However, concern regarding insulin resistance should not be limited to the type 2 diabetes population, because 42% of the CHD attributable to insulin resistance is among those without type 2 diabetes. The current model indicates that identification and treatment of individuals with insulin resistance may yield significant clinical and economic benefits.

The relationship between insulin resistance and CHD requires further research. If the results of ongoing studies support current evidence, a large number of annual CHD events and their subsequent costs can be appropriately targeted for intervention. The use of insulin resistance as a marker for risk of CHD would provide an additional means of identifying and treating individuals at risk for CHD events. Earlier identification of those at risk for CHD events would provide opportunities for early interventions and improved quality of care. Improving insulin sensitivity would offer substantial benefits by decreasing the morbidity, mortality, and costs associated with CHD in the United States.

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