

Relationship of Insulin Resistance and Related Metabolic Variables to Coronary Artery Disease: A Mathematical Analysis

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OBJECTIVE — People with diabetes have an increased risk of coronary artery disease (CAD). An unanswered question is what portion of CAD can be attributed to insulin resistance, related metabolic variables, and other known CAD risk factors.

RESEARCH DESIGN AND METHODS — The Archimedes model was used to estimate the proportion of myocardial infarctions that would be prevented by maintaining insulin resistance and other risk factors at healthy levels. Person-specific data from the National Health and Nutrition Examination Survey 1998–2004 were used to create a simulated population representative of young adults in the U.S. This population was then entered into a series of simulated clinical trials designed to explore the effects of each risk factor. Each trial had a control arm (all risk factors were allowed to progress without interventions) and a treatment arm (a risk factor was held to its value in young healthy adults). The trials continued for 60 years. The effects of these hypothetical “cures” of each risk factor provide estimates of their impact on CAD.

RESULTS — In young adults, preventing insulin resistance would prevent ~42% of myocardial infarctions. The next most important determinant of CAD is systolic hypertension, prevention of which would reduce myocardial infarctions by ~36%. Following systolic blood pressure, the most important determinants are HDL cholesterol (31%), BMI (21%), LDL cholesterol (16%), triglycerides (10%), fasting plasma glucose and smoking (both ~9%), and family history (4%).

CONCLUSIONS — Insulin resistance is likely the most important single cause of CAD. A better understanding of its pathogenesis and how it might be prevented or cured could have a profound effect on CAD.

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Considerable research has been done to understand the effects of insulin resistance on metabolism in different tissues (e.g., liver, muscle, and fat), inflammation, and other important biological processes. Downstream from these adverse effects of insulin resistance are clinically measured abnormalities such as hypertension and dyslipidemia (e.g., high triglyceride levels and low HDL cholesterol levels). Thus, through its effects on these and other variables, insulin resistance could be the underlying cause of

much of coronary artery disease (CAD) (1,2).

To derive the greatest clinical value from the research outlined above, it is important to understand the relative role of insulin resistance in CAD compared with other well-known cardiovascular risk factors that may exist independently of insulin resistance. For example, if insulin resistance could be prevented, how much CAD would be prevented? What is the effect of obesity on CAD as mediated through insulin resistance? What propor-

tion of CAD is caused by other risk factors such as LDL cholesterol, C-reactive protein, and blood pressure and by nonmetabolic risk factors such as age, sex, and race/ethnicity? Answers to these questions are important for identifying targets and priorities for treatments, for understanding the potential effects of interventions that specifically reduce insulin resistance such as exercise and weight loss, and for simply understanding the etiology of CAD.

Ideally, to determine the effects of any particular variable on CAD, one would conduct a clinical trial in which the variable was controlled to its normal level. No such trials exist or are possible until treatments are developed that specifically and only target the variable in question. In the absence of such trials, insights can be gained from combining the results of the research that already exists. This can be done mathematically; mathematical models are the only method available for integrating the results of the research conducted to date to help further our understanding of the biological pathways and the relative causes of adverse outcomes.

This paper describes such an approach. Specifically, we used existing research to develop a mathematical representation of current theories of the physiological pathways that relate diabetes and other metabolic and nonmetabolic variables to CAD. We then used the model to simulate the trials that would ideally be conducted to examine the effects of each variable, if that were possible. We used this approach to estimate the effects on CAD events (fatal and nonfatal myocardial infarctions) of the following variables: insulin resistance, obesity, HDL cholesterol, LDL cholesterol, triglycerides, systolic blood pressure (SBP), smoking, age, sex, and race/ethnicity. We also examined the possible causal roles of free fatty acid (FFA), apolipoprotein B (apoB), lipoprotein(a), C-reactive protein, and homocysteine.

RESEARCH DESIGN AND METHODS

For this analysis, we constructed a model of diabetic dyslipidemia based on pathways described by

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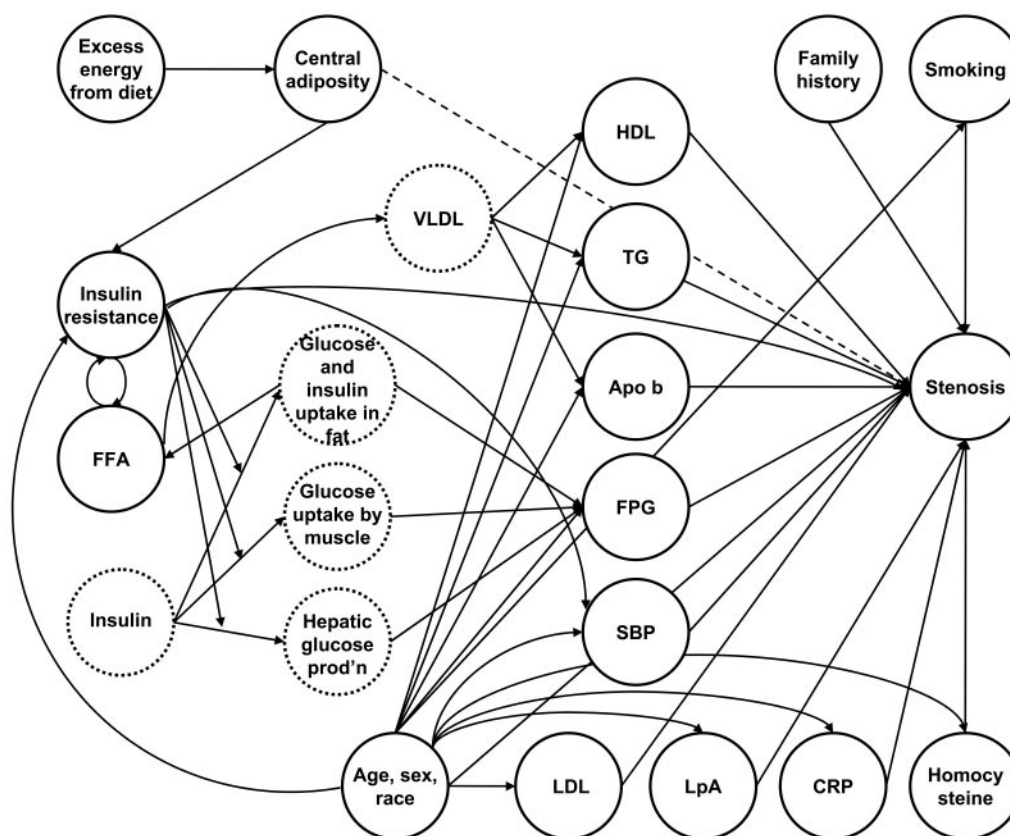


Figure 1—Variables and pathways in the Archimedes model pertinent to coronary artery disease. Variables in solid circles are calculated for this analysis. CRP, C-reactive protein; prod'n, production; TG, triglyceride.

Ginsberg (3) (Fig. 1). Briefly, excess energy intake is stored in fat and liver, causing central adiposity. This decreases the effects of insulin on uptake of glucose in muscle and fat and production of glucose by the liver (insulin resistance). This in turn increases plasma glucose levels. Insulin resistance in adipocytes results in greater release of FFA from fat into the circulation. The resulting increased FFA flux to liver increases synthesis of VLDL cholesterol (4), resulting in increased levels of triglycerides and apoB, smaller and denser LDL cholesterol, and decreased availability of HDL cholesterol. FFA also increases insulin resistance in liver (5,6). While there is some evidence that FFAs may influence CAD risk through additional mechanisms, such as endothelial dysfunction (7), hypercoagulation, impaired fibrinolysis (8,9), and increased blood pressure, these effects are not quantifiable at this time. Figure 1 also shows the effects of other variables and risk factors that contribute to CAD.

The analysis was conducted using the Archimedes model (10,11). Briefly, the model is a person-by-person, object-by-object simulation written at a relatively

high level of biological, clinical, and administrative detail using object-oriented programming. The core of the model is a set of continuous equations that represent the physiological pathways pertinent to diseases, such as those illustrated in Fig. 1. Currently, CAD, diabetes and its complications, congestive heart failure, stroke, obesity, smoking, and metabolic disorders are included in a single integrated model, enabling it to address comorbidities and syndromes in a realistic way. Variables in the model pertinent to this analysis are shown in Fig. 1. For CAD, the model includes both gradual and sudden occlusion of coronary and cerebral arteries. The use of differential equations preserves the continuous nature of biological variables.

To conduct simulations, the Archimedes model creates virtual people, each of whom has his or her own simulated physiology and can get diseases, develop symptoms, seek care, and so forth. To ensure that the virtual people are representative of real people, the Archimedes model creates copies of real people using person-specific data from datasets such as the National Health and Nutrition Exam-

ination Survey (NHANES), health risk appraisals, personal health records, and electronic medical records. It does this at the level of detail captured in the dataset including, if available, demographic characteristics, physical examination results, behaviors, family history, current medical conditions, past medical history, biological variables (lab results), symptoms, and current medications. The methods for creating copies ensure that the distributions and correlations of all of the important variables are the same in the simulated population as in the real population.

In the model, when patients seek care, providers apply protocols and follow guidelines for tests and treatments. Test results are functions of the underlying variables being measured and can have systematic and random errors. Interventions are modeled through their effects on the underlying biological variables. Simulated providers have behaviors that affect their performance and practice patterns. Simulated patients have behaviors relating to seeking care and adhering to treatment recommendations. Because the model is continuous in time,

symptoms and the ensuing clinical events can occur at any time and are different for every patient. Care processes pertinent to this analysis were based on guidelines of the American Diabetes Association and American Heart Association.

We validate the model using methods described elsewhere (12,13). Briefly, we use the model to simulate real clinical trials and compare the simulated and real results. To date, this has been done for 48 clinical trials relating to diabetes and CAD. Results of the first 18 trials have been published (12).

The variables and pathways in the model that are most pertinent to diabetes and CAD are shown in Fig. 1, with the arrows indicating equations that relate the variables to each other and to the progression of atherosclerosis. In the model, the insulin resistance variable represents not only the resistance of fat, muscle, and liver to the effects of insulin but also the change in production of insulin by pancreatic β -cells (initial β -cell compensation and eventual β -cell fatigue). In the model, insulin resistance affects not only glucose but other risk factors for CAD, such as SBP, HDL cholesterol, triglycerides, and apoB. Equations relating insulin resistance with these variables were estimated from data derived from the UK Prospective Diabetes Study (14,15) for glucose, from NHANES (1998–2004) for triglycerides and HDL cholesterol, and from data on blood pressures in various populations of people with and without diabetes (16). Other variables and sources are described elsewhere (17).

For this analysis, our objective was to estimate the effects of the variables in Fig. 1. Our approach was to simulate the clinical trials that would ideally be performed if they were possible: treat each variable one by one to its normal value and measure the change in CAD events over a long period of time. The results provide an estimate of the proportion of CAD “caused” by each variable, taking into account its effects on other variables downstream in the physiological pathways (Fig. 1). For example, for the simulated trial for insulin resistance, we created a hypothetical treatment that maintained the effects of insulin on liver, fat, and muscle at their normal levels. The normalization of the effects of insulin then affected downstream variables such as triglycerides and HDL cholesterol, which in turn affected the development of atherosclerotic plaque and myocardial infarctions.

Table 1—Treatment targets for variables and percent decrease in incidence of MIs as a result of normalizing variable values to reach treatment targets

| | Target for normalization | Decrease in incidence of MIs (fatal and nonfatal) |
|-----------------------------|-----------------------------------|---|
| Insulin resistance | Average value at ages 20–30 years | 42 |
| SBP (mmHg) | 114 | 36 |
| HDL cholesterol (mg/dl) | 46 (men), 54 (women) | 31 |
| BMI (kg/m ²) | 22.5 | 21 |
| LDL cholesterol (mg/dl) | 108 | 16 |
| Triglycerides (mg/dl) | 108 | 10 |
| FPG (mg/dl) | 86 | 9 |
| Smoking | Never smoke | 9 |
| Family history | No family history | 4 |
| Causality not established | | |
| FFA (mg/dl) | 20 | 18 |
| C-reactive protein (mg/dl) | 0.32 | 10 |
| ApoB (mg/dl) | 85 | 9 |
| Lipoprotein(a) (mg/dl) | 57 (blacks), 21.5 (nonblacks) | 9 |
| Homocysteine (μ mol/l) | 7.0 | 5 |
| All variables | NA | 94 |

Data for decrease in myocardial infarction are percent. Treatment targets represent the average values for people aged 20–30 years in the U.S. population. NA, not applicable.

For the simulated trials, we used person-specific data from the 1998–2004 NHANES survey to create a simulated population representative of young adults aged 20–30 years in the U.S. (18). For each simulated trial, we created a control arm in which the subjects were followed with no treatments for CAD prevention. This arm determined the natural, untreated progression of CAD to the point of an event (fatal and nonfatal myocardial infarction). Each trial also included a hypothetical treatment in which the variable of interest was controlled as soon as it became abnormal compared with a target value intended to represent good health. To determine the target values that represent good health, we used the average values for people aged 20–30 years in the U.S. today (from NHANES)—with one exception. The average BMI in people aged 20–30 years in the U.S. is 26 kg/m², which is generally considered overweight. Rather than using this as the value to represent good health, we arbitrarily chose a value of 22.5 kg/m².

The values for young adults obtained by this method are shown in the first data column of Table 1. We call these “normal” values and use the term “abnormal” to describe values above (or, in the case of HDL cholesterol, below) these levels. We use the term “normalize” to describe a protocol that tests everyone annually, identifies people whose values of a variable exceed

(or, in the case of HDL cholesterol, fall below) the normal value, and then treats those people to the normal values. Treatments were hypothetical and designed to control variables precisely such that they reach the normal level. In this sense, the treatments were analogous to clamp studies or knockout mice. Treatment of any particular variable would affect any downstream variables, as illustrated in Fig. 1. People with values below (or, in the case of HDL cholesterol, above) the normal values were not treated. For the five new variables added to the model, we conducted “what-if” trials in which we calculated their possible effects on CAD on the assumption that the variables are causal, just to determine the possible magnitudes of their effects.

Each simulated trial was conducted using the same 10,000 simulated people for both the treatment and control arms for a given trial. Subjects were followed for 60 years or until they died. All the pertinent variables and outcomes were measured annually. Although a large number of outcomes were recorded, for this analysis we used the cumulative probability of fatal and nonfatal myocardial infarction (including repeat myocardial infarctions) as the primary end point.

RESULTS—As calculated by the model, young adults aged 20–30 years in the U.S. today have about a 43% lifetime

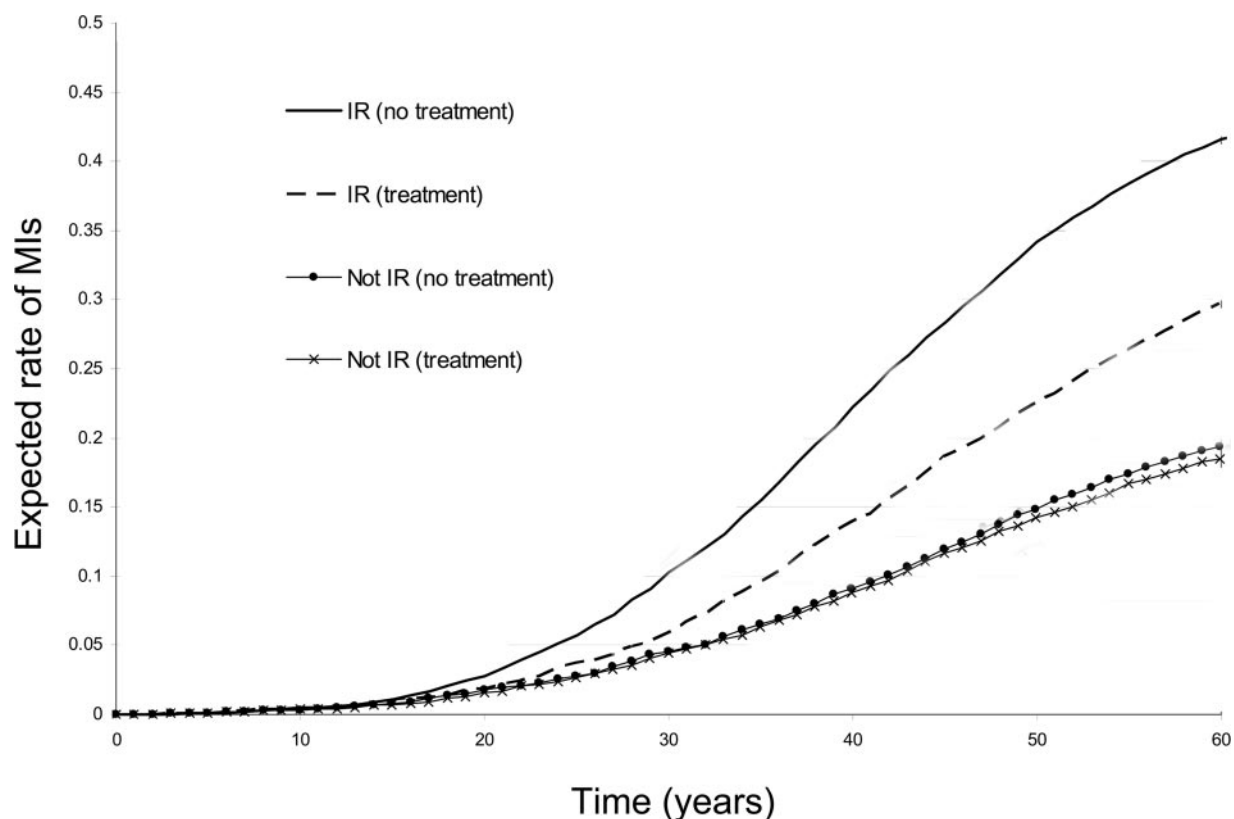


Figure 2—Effect of curing insulin resistance (IR) on the expected rate of fatal and nonfatal myocardial infarctions (MIs) for people destined or not destined to develop insulin resistance.

rate of fatal or nonfatal myocardial infarctions (95% CI 42–44). The effects of normalizing insulin resistance on myocardial infarctions are shown in the right column of Table 1; normalization prevents approximately 42% of myocardial infarctions. Figure 2 shows the rates of myocardial infarctions in people who are destined to get insulin resistance and those who are not. Approximately 50% of young adults are destined to get some degree of insulin resistance, although insulin resistance progresses to the point at which diabetes develops in less than one-fifth of young adults. Those who are destined to develop some degree of insulin resistance face nearly three times greater risk of CAD than those who are not. In people who are destined to develop insulin resistance, normalizing insulin resistance reduces the risk by approximately 55%.

The effects of insulin resistance are also affected by sex. Today's young men face a higher rate of myocardial infarctions than today's young women: 55 vs. 32%. However, insulin resistance plays a larger relative role in women than in men, with normalization of insulin resistance reducing the myocardial infarction rate

~57% for women (from 32 to 14%), compared with ~29% (from 55 to 39%) for men.

The effects of other variables on myocardial infarctions are shown in Table 1. As causes of CAD, they range from high SBP (determining ~36% of CAD) to family history (responsible for ~4%). The five new variables for which causality was assumed are shown in the bottom half of Table 1. If they are eventually established to be causal, normalizing them should decrease CAD rates by the amounts shown in the table. Otherwise, the values in the table for these variables indicate the proportions of CAD risk for which they are markers.

CONCLUSIONS— In this study, we estimate the proportion of CAD due to insulin resistance, other metabolic variables, and other cardiovascular risk factors. Our analysis takes into account the large number of people who develop some degree of insulin resistance, the long time course of developing insulin resistance, the pathological effects of a low degree of insulin resistance, and the effects of insulin resistance on other metabolic variables.

Of the risk factors that we believe are sufficiently well studied to permit quantitative analysis, insulin resistance is the most important single risk factor for CAD. Our results indicate that insulin resistance is responsible for approximately 42% of myocardial infarctions. Its effect on CAD is indirect, mediated through its effects on other variables such as SBP, HDL cholesterol, triglycerides, glucose, and apoB. Each of those variables, in turn, is affected by other variables such as age, sex, and race/ethnicity. If each risk factor is considered by itself, the next most important cause of CAD is high SBP; normalization of SBP would prevent ~36% of myocardial infarctions. After SBP are HDL cholesterol (31%), BMI (at least 21%), LDL cholesterol (16%), triglycerides (10%), fasting plasma glucose (9%), smoking (9%), and family history (4%).

Our analysis also highlights the role of obesity in the etiology of both diabetes and CAD. There is good evidence that obesity is a major cause of insulin resistance, and through insulin resistance, obesity affects blood pressure, triglycerides, HDL cholesterol, fasting plasma glucose, and apoB. Just by these effects,

insulin resistance is a powerful risk factor for CAD; in our analysis, normalizing BMI at 22.5 kg/m² would prevent more than one-fifth of myocardial infarctions in the U.S. (Table 1). Beyond this, it is possible that obesity has other direct effects on CAD that are not represented in our model.

Our results are not directly comparable with those of clinical trials, where the effects of glucose lowering on CAD were either much smaller (19,20,21) or null (22,23). The reason is that in the clinical trials, the focus was on lowering blood glucose—not preventing or curing insulin resistance. The drugs used in the trials either lowered glucose without affecting insulin resistance (e.g., sulfonylureas and insulin) or lowered insulin resistance to some extent but did not eliminate it (e.g., metformin and rosiglitazone). Furthermore, we normalized insulin resistance over the entire lifetimes of the subjects, whereas the treatments in the trials were given only after individuals had developed diabetes and were given only for the limited durations of the studies. Thus, the results of the trials do not represent the full effect of normalizing insulin resistance and are actually consistent with our results.

Our finding that insulin resistance is responsible for 42% of CAD suggests the possible value of a 100% effective treatment of insulin resistance, should there eventually be one. Although insulin resistance can be ameliorated by weight loss, our data indicate that other interventions will be needed. Increased physical activity, diet modification, and drug therapy are obvious approaches, although we could not model the effects of these interventions on insulin resistance because their quantitative effects are unknown or unclear. Also, as we come to better understand the underlying etiology and effects of insulin resistance (e.g., its relationship with FFA flux [24] or the inflammatory process [25]), new interventions to prevent or treat insulin resistance or factors upstream from it will likely be developed.

Our results indicate that because of the effects of obesity on insulin resistance, curing obesity could be expected to prevent at least 21% of myocardial infarctions. Thus, interventions that prevent excess weight gain or maintain weight loss should have a major effect on CAD. Because of insufficient data, we could not model the separate effects of visceral obesity, ectopic fat, or other measures of weight-related metabolic abnormalities.

The main limitation of this analysis is that it is based on a mathematical model rather than on empirical studies. We have tried to make the model as realistic and accurate as possible by reproducing current theories of metabolic pathways, by ensuring that each equation is derived from and validated against empirical evidence, and by testing the accuracy of the full set of equations by calculating the occurrence of diabetes and CAD in a wide variety of clinical trials. Based on these validations, it is reasonable to say that the model is entirely consistent with the best available published evidence. Nonetheless, our analysis is limited to variables for which there are data sufficiently good for writing and validating equations. In the Archimedes model, data must not only establish a qualitative relationship between variables but also enable writing and validating equations that describe that relationship quantitatively. It is possible that a relationship between variables exists but cannot yet be described quantitatively from the available data.

Our results also depend on the targets chosen for treating the variables. For family history and smoking, the targets are obvious: eliminate the effects of family history and have people stop smoking. But other variables are continuously valued, and there are no levels that can unequivocally be designated “normal,” “healthy,” or “cured.” We had to specify the targets to which the variable values would be controlled. Possible choices were the thresholds that organizations use to define diseases such as diabetes or the treatment targets used in national guidelines or performance measures. We chose not to use any of these because in addition to being inconsistent with one another, they are all considerably higher than average values, often representing top quartiles or quintiles, and they typically represent people with moderately advanced disease. Instead, we chose as targets the average values of people in the U.S. aged 20–30 years on the assumption that this better represents a healthy, non-diseased state.

This modeling exercise has important practical implications. It addresses the relative importance of well-known variables in the genesis of CAD and suggests areas that should be the focus of research and treatment. More specifically, our results indicate that insulin resistance itself has a profound effect on CAD—greater than previously realized. In fact, it is likely the most important single determinant of

CAD. Additional research into the underlying pathogenesis of insulin resistance and its downstream effects, prevention, and cure should receive high priority for the prevention of CAD.

Ideally, the questions we address in this paper would be answered through empirical research. Unfortunately, that is not possible. There is no way to normalize insulin resistance, get everyone to stop smoking, or implement most of the other interventions required. Even if the interventions existed, the empirical studies would be infeasible because of size, duration, cost, and speed of technological change. Yet, the questions are undeniably important. A physiology-based model is the best available alternative. It is consistent with and works hand in hand with the available research. It converts the observations that have been made and the theories that have been developed into a form that can be used to estimate the approximate magnitudes of outcomes, stimulate debate and research, and begin a cycle that should gradually converge on a deeper and more accurate understanding of physiological pathways than would otherwise be possible.

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