The Contribution of Autonomic Imbalance to the Development of Metabolic Syndrome

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ABSTRACT

Objectives: Obesity, diabetes, and heart disease—the most costly epidemics of our time—share a common but rarely treated mechanism: autonomic imbalance. We examined the contribution of autonomic imbalance, relative to selected demographic and biobehavioral risk factors, to the development of metabolic syndrome in a community sample for 12 years.

Methods: We identified offspring cohort participants from the Framingham Heart Study who did not have metabolic syndrome at Examination 3 (1983–1987, baseline for this analysis) and whose metabolic syndrome status was assessed at the 4-, 8-, and 12-year follow-ups. We created logistic regression models, using baseline resting heart rate (RHR) and heart rate variability (HRV), to predict the odds of developing metabolic syndrome within 12 years, adjusting for age, sex, depressive symptoms, and smoking. HRV indices (standard deviation of the beat-to-beat interval [SDNN] and root mean square of the standard deviation) were calculated from 2-hour Holter monitor data.

Results: Our sample consisted of 1143 participants (mean [SD] age = 46.6 (9.9) years, 57% female). One standard deviation of a decrease in SDNN increased the odds of developing metabolic syndrome within 12 years by 43% (95% confidence interval = 1.302–1.572, \( p < .001 \)). Without HRV in the model, each increase in RHR of 10 beats/min increased the odds of developing metabolic syndrome by 24% (95% confidence interval = 1.094–1.426, \( p < .001 \)).

Conclusions: In this community sample, low HRV by both measures (SDNN and root mean square of the standard deviation), high RHR, increased age, cigarette smoking, and being male significantly increased the odds of developing metabolic syndrome within 12 years of baseline.

Key words: heart rate, heart rate variability, metabolic syndrome, risk factors, epidemiology.

INTRODUCTION

Although metabolic disorders, such as diabetes and coronary heart disease, commonly begin as clusters of metabolic risk factors, often called the metabolic syndrome (Table 1) (1), only two published studies have examined predictors of the metabolic syndrome (2,3). The condition affects more than one-third of the adult population in the United States (4) and is associated with an increased risk of incident coronary heart disease (5–7) and Type 2 diabetes (4,8), as well as with an increased risk of all-cause mortality and coronary heart disease mortality (4,6,9,10). Moreover, people with metabolic syndrome require 1.6 times the health care expenditures of persons without the condition, with an average annual cost increase of 24% per subsequent metabolic syndrome component (11).

One candidate pathway to metabolic syndrome and later metabolic disorders is through autonomic imbalance, namely, excessive sympathetic activity and too little parasympathetic activity (12). Although ignored by most clinicians, autonomic imbalance is a common but rarely treated condition, and it is the only mechanism associated with all eight major cardiovascular risk factors, including obesity and diabetes (12). Autonomic imbalance can be measured and treated by a variety of methods often used...
Because WC was not available at baseline, we substituted body mass index for this component and used the cutoff of 25 or higher.

In two cross-sectional studies, researchers found an association between autonomic imbalance and metabolic syndrome. In their analysis of the baseline assessment of a longitudinal community study in the Netherlands, Licht and colleagues (13) compared two possible contributing factors, autonomic imbalance and hypothalamic-pituitary-adrenal axis activity, to the presence and severity of metabolic syndrome. Although hypothalamic-pituitary-adrenal axis measures were not related to metabolic syndrome, three measures of autonomic imbalance, including heart rate and heart rate variability (HRV), were related to the presence of metabolic syndrome and the number of component conditions, and independently to each individual condition. Parallel decreases in parasympathetic and increases in sympathetic activity characterized the autonomic imbalance.

In addition, in the Twins Heart Study, Gehi and colleagues (14) examined the association between HRV and metabolic syndrome in 288 twins. Controlling for genetic and shared environmental factors, the metabolic syndrome was associated with decreased HRV across four of five frequency ranges, and each additional metabolic syndrome condition was associated with lower HRV. The authors concluded that, “abnormalities of autonomic tone…may be partly responsible for the higher rate of atrial fibrillation, coronary heart disease, cardiac death, and overall mortality seen in patients with the MetS” (pp. 422).

Jarczok and colleagues (15) found a significant negative correlation between HRV and glycemic status in a sample of 2441 healthy workers, after adjusting for metabolic syndrome components. In a report from the Atherosclerosis Risk in Communities Study, Liao and colleagues (16) found an association between low HRV and multiple metabolic disorders, namely, hypertension, dyslipidemia, and Type 2 diabetes.

Franco and colleagues (2) published the first prospective study of predictors of the development of metabolic syndrome.

In their secondary analysis of the Framingham Heart Study (FHS) offspring cohort (N = 3078), they focused on first conditions of metabolic syndrome as predictors. The prevalence of metabolic syndrome almost doubled in 10 years, from 23.5% to 40.6%. Central obesity conferred the highest risk of developing metabolic syndrome (odds ratio [OR] = 4.75, 95% confidence interval [CI] = 3.78–5.98) and, in women who developed metabolic syndrome, hypertension tended to be the first condition to appear, whereas in men, low high-density lipoprotein appeared first. They also identified specific combinations of metabolic conditions, which conferred higher risk for cardiovascular disease and death. However, the researchers did not examine whether or not autonomic imbalance predicted metabolic syndrome in this sample.

In the second prospective study of predictors of metabolic syndrome, Licht and colleagues (3) reported in 2013 on their 2-year follow-up of their Netherlands longitudinal sample. They found that four measures of autonomic imbalance predicted increases in the number of conditions of metabolic syndrome. Specific autonomic imbalance measures predicted increases in blood pressure or decreases in high-density lipoprotein cholesterol. They concluded that their findings “suggest that a dysregulation of the autonomic nervous system is an important predictor of cardiovascular disease and diabetes through dysregulating lipid metabolism and blood pressure over time.”

These studies provide compelling reasons to investigate the effects of autonomic imbalance, relative to selected demographic and biobehavioral risk factors, on the development of metabolic syndrome. Our study extends the work of Licht and colleagues by assessing the contribution of two measures of autonomic imbalance on the incidence of metabolic syndrome for 12 years in a community sample. We conducted a secondary analysis of an existing data set, the offspring cohort of the FHS. We assessed autonomic imbalance at baseline (1983–1987) and metabolic syndrome 4, 8, and 12 years later. We hypothesized that autonomic imbalance at baseline, adjusted for age, sex,
smoking, and depressive symptoms, would significantly increase the odds of developing metabolic syndrome within 12 years.

**METHODS**

**Participants**

Participants included the offspring cohort from the FHS. The offspring cohort was first examined in 1971 to 1975 and approximately every subsequent 4 years. We included participants who met the following criteria at baseline at the third examination (1983–1987): a) were 18 years or older and b) had data on resting heart rate (RHR), HRV, and metabolic syndrome components (n = 1882).

We then excluded participants who had metabolic syndrome (n = 539), or their metabolic syndrome status was unknown (n = 1), at baseline. We also excluded participants whose metabolic syndrome status was unknown for any of the three follow-up time points (n = 197), as well as excluded participants who did not have data on one of the baseline covariates: smoking (n = 2).

The remaining sample (n = 1143) included participants whose metabolic syndrome status was either positive at one or more of the 4-, 8-, or 12-year follow-ups (“ever”), or was negative at all three follow-ups (“never”). See Figure 1.

**Measures**

**Autonomic Imbalance**

Of the many available measures of autonomic imbalance (17), we focused on two measures: RHR and HRV. These measures appear commonly in the literature and are obtainable through primary care settings. For RHR, we used the heart rate from the EKG, which was performed on each participant during the baseline clinic examination (1983–1987). For HRV, we abstracted from the baseline 2-hour Holter monitor data all available measures of variability and focused our analyses on the standard deviation of beat-to-beat intervals (SDNN), one of the more commonly reported indices of HRV. The range of Pearson correlations between SDNN and the other common measures of HRV in this sample was from 0.60 to 0.82, all significant at less than .001. Recognizing that SDNN reflects all sources of HRV, including both the sympathetic and parasympathetic nervous system activities, we conducted supplementary analyses using the root mean square of the standard deviation (RMSSD), a measure that more narrowly reflects parasympathetic activity only.

**Metabolic Syndrome**

We classified metabolic syndrome using the consensus definition from several national and international organizations (1). The metabolic syndrome criteria are listed in Table 1. Because waist circumference (WC) was not available at baseline, we substituted body mass index (BMI) for this component and used the cutoff of 25 or higher. In our study, the correlations between WC and BMI at the follow-up time points were greater than 0.80, and in another study (18), the correlation between WC and BMI was greater than 0.90.

**Other Contributing Factors**

To examine the relative contributions of other demographic and biobehavioral factors to metabolic risk, we selected covariates in our model for which reliable measures exist in the FHS offspring database and which are known to be related to metabolic risks: sex, age, cigarette smoking (cigarettes per day), and current (past week) depressive symptoms as measured by the Center for Epidemiologic Studies-Depression Scale (19). Although potentially important, we did not include physical activity, insulin resistance, or C-reactive protein because these variables were not collected at baseline.

**Analyses**

We conducted a backward elimination variable selection procedure on a logistic regression model, using the dichotomous variable of metabolic syndrome status at any time after baseline as the outcome variable. We used the independent baseline variables of autonomic imbalance (RHR and HRV) and the covariates of age, sex, cigarette smoking, and their second-order interactions with autonomic imbalance, to predict the odds of developing metabolic syndrome within 12 years. (Data on depressive symptoms did not contribute to any of the models and so are not presented here; they are available on request.)

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**FIGURE 1.** Selection flowchart. MetS = metabolic syndrome.
Model selection was determined by area under the receiver operating characteristic curve (AUC) and Hosmer-Lemeshow goodness-of-fit (GOF) test $p$ value. The AUC is a number between zero and one and measures the descriptive/predictive value of the model—the larger the AUC, the better the model; an AUC of 0.5 or less indicates poor predictive ability. The GOF test measures the overall appropriateness of a given model—the larger the $p$ value, the more appropriate the particular logistic model, because the null hypothesis is that the particular logistic regression model is the appropriate model. A GOF $p$ value of .1 or greater is considered adequate. We also examined a model that included RHR alone as a predictor, without HRV. Analyses were conducted using the SAS statistical software package version 9.2 (SAS Institute, Inc, Cary, NC), and the significance level used in retaining variables in the models was set at $\alpha = .05$.

RESULTS

Our sample (Table 2) consisted of 1143 participants, nearly all of whom were white. The baseline age was 46.6 ± 9.9 years, there were more women than men (57% versus 43%), and the baseline cigarettes smoked was 5.6 ± 11.5 cigarettes per day. The baseline RHR was 64.4 ± 9.9 beats/min, and the baseline HRV (SDNN) was 0.099 ± 0.027 milliseconds.

As a result of the variable selection procedure, we settled on a simple model consisting of the predictors of HRV (SDNN), age, sex, and cigarette smoking (Table 3). The intercept and interaction terms with SDNN were not statistically significant. The AUC was equal to 0.666 and the GOF $p$ value was .74. One standard deviation of a decrease in SDNN increased the odds of developing metabolic syndrome within 12 years by approximately 43% (OR = 1.43, 95% CI = 1.302–1.572). In addition, for each increase in age by 1 year and for each cigarette smoked, the odds of developing metabolic syndrome within 12 years increased by 2.8% and 2.0%, respectively (age: 95% CI = 1.4%–4.1%, $p < .001$; cigarettes: 95% CI = 0.9%–3.2%, $p < .001$). Finally, the odds of developing metabolic syndrome within 12 years of baseline was 2.2 times higher for men than for women (95% CI = 1.71–2.81, $p < .001$). Figure 2 illustrates the probability of developing metabolic syndrome in relationship to HRV (SDNN) for each sex evaluated at the mean age and number of cigarettes smoked.

In the original variable selection procedure, RHR did not enter the model because HRV (SDNN) was consistently a stronger predictor. However, when we analyzed the model without SDNN, RHR was a significant predictor of ever having metabolic syndrome (Table 4). For each increase in RHR of 10 beats/min, the odds of developing metabolic syndrome increased by 24% (95% CI = 9.4%–42%, $p < .001$). The effect of sex and cigarettes on risk of developing metabolic syndrome was similar in this model to their effect in the HRV model. The only significant interaction variables in both models were age related (although the age-by-HRV interaction was significant, the ORs were <1 regardless of age), and the inclusion of significant interaction variables did not improve the model. In comparison to the HRV model, the RHR model was slightly worse (lower $p$ value) with respect to GOF (HRV [SDNN] GOF = 5.22, $p = .74$ versus RHR GOF = 11.22, $p = .19$, $df = 8$).

Because in the final models smoking and HRV (SDNN) or RHR were the only modifiable variables, we considered it potentially clinically important to examine these relationships among nonsmokers, who constituted 73% of the sample. Among the nonsmokers ($n = 846$), HRV (SDNN), age, and sex predicted the development of metabolic syndrome within 12 years after baseline and substituting RHR for HRV (SDNN) in the same model resulted in adequate AUC and GOF values (see Tables S1 and S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A262).

To examine the contribution of low parasympathetic activity to the development of metabolic syndrome, in supplementary analyses, we substituted for SDNN the RMSSD, a

<table>
<thead>
<tr>
<th>TABLE 2. Baseline Variables ($n = 1143$)</th>
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<tbody>
<tr>
<td>Variables</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Cigarettes (per day)</td>
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<tr>
<td>Resting heart rate, beats/min</td>
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<tr>
<td>Heart rate variability</td>
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<tr>
<td>SDNN, s</td>
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<td>RMSSD, s</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Smokers</td>
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$M =$ mean; $SD =$ standard deviation; $SDNN =$ standard deviation of the beat-to-beat interval; $RMSSD =$ root mean square of the standard deviation.

<table>
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<tr>
<th>TABLE 3. Odds Ratio Estimates for Ever Developing Metabolic Syndrome</th>
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<tbody>
<tr>
<td>Variables</td>
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<tr>
<td>Sex, male$^a$</td>
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<tr>
<td>Cigarettes$^b$</td>
</tr>
<tr>
<td>Age$^c$</td>
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<tr>
<td>HRV SDNN$^d$</td>
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</tbody>
</table>

OR = odds ratio; HRV = heart rate variability; SDNN = standard deviation of the beat-to-beat interval; AUC = area under the receiver operating curve. AUC = 0.666.


$^a$ The odds of a man ever developing metabolic syndrome is 2.191 times greater than that of a woman.

$^b$ OR per cigarette smoked.

$^c$ OR per year of age.

$^d$ OR per 1 standard deviation decrease in HRV SDNN.
measure commonly considered to capture the parasympathetic activity of the autonomic nervous system. HRV (RMSSD) continued to contribute significantly (OR = 0.868, 95% CI = 0.762–0.988, p = .032) to incident metabolic syndrome (Table 5).

DISCUSSION
In this community sample of middle-aged men and women, low HRV, increased age, cigarette smoking, and being male significantly increased the odds of developing metabolic syndrome within 12 years of baseline. The magnitude of the effect in Figure 2 suggests that, as HRV (SDNN) drops by half, the risk of developing metabolic syndrome more than doubles. Moreover, in terms of the risk of developing metabolic syndrome within 12 years of baseline, one standard deviation decrease in HRV (SDNN) is equal to an additional 16 years in age or nearly one pack of cigarettes per day. In other words, autonomic imbalance, as measured by HRV (SDNN), seems to contribute a substantial effect on the risk for developing metabolic syndrome, as substantial perhaps as age and smoking. Adding HRV (SDNN) to a model of age, sex, and cigarettes substantially improves the prediction of metabolic syndrome, whereas adding RHR does not.

These findings support a possible role for autonomic imbalance in the development of metabolic risk and its consequences, such as diabetes and heart disease. However, although autonomic imbalance independently predicts the development of metabolic syndrome, it is not yet clear whether or not autonomic imbalance plays a causal role in the development of metabolic syndrome or its consequent conditions.

Franco and colleagues (2) found in this same cohort that, among first metabolic conditions to appear, central obesity confers the highest risk for the later development of metabolic syndrome. Our results suggest that low HRV may also contribute to the prediction of metabolic syndrome, especially in men and smokers. Also, among nonsmokers in our study, an increase of one standard deviation of HRV

<p>| TABLE 4. Odds Ratio Estimates for Ever Developing Metabolic Syndrome (Omitting HRV) |</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% Confidence Limits</th>
<th>p</th>
</tr>
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<tr>
<td>Sex, male&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.275</td>
<td>1.767–2.929</td>
<td>&lt;.001</td>
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<td>Cigarettes&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>1.010–1.032</td>
<td>&lt;.001</td>
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<tr>
<td>Age&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.035</td>
<td>1.022–1.048</td>
<td>&lt;.001</td>
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<tr>
<td>RHR&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.244</td>
<td>1.094–1.416</td>
<td>&lt;.001</td>
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</tbody>
</table>

HRV = heart rate variability; OR = odds ratio; RHR = resting heart rate; AUC = area under the receiver operating curve.
<sup>a</sup>The odds of a man ever developing metabolic syndrome is 2.275 times greater than that of a woman.
<sup>b</sup>OR per cigarette smoked.
<sup>c</sup>OR per year of age.
<sup>d</sup>OR per 10 beats/min of RHR.
AUC = 0.657.

<p>| TABLE 5. Odds Ratio Estimates for Ever Developing Metabolic Syndrome |</p>
<table>
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<tr>
<th>Variables</th>
<th>OR</th>
<th>95% Confidence Limits</th>
<th>p</th>
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<td>Sex, male&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.070</td>
<td>1.622–2.642</td>
<td>&lt;.001</td>
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<tr>
<td>Cigarettes&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>1.012–1.034</td>
<td>&lt;.001</td>
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<tr>
<td>Age&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.031</td>
<td>1.017–1.044</td>
<td>&lt;.001</td>
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<tr>
<td>HRV RMSSD&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.153</td>
<td>1.012–1.313</td>
<td>.032</td>
</tr>
</tbody>
</table>

OR = odds ratio; HRV = heart rate variability; RMSSD = root mean square of the standard deviation; AUC = area under the receiver operating curve.
<sup>a</sup>The odds of a man ever developing metabolic syndrome is 2.070 times greater than that of a woman.
<sup>b</sup>OR per cigarette smoked.
<sup>c</sup>OR per year of age.
<sup>d</sup>OR per 1 standard deviation decrease in HRV RMSSD.
AUC = 0.652.

FIGURE 2. Probability of developing metabolic syndrome as a function of baseline HRV (SDNN). HRV = baseline heart rate variability; SDNN = standard deviation of the N-N interval, in seconds.
(SDNN) predicted a 25% decrease in risk for metabolic syndrome. Among the nonsmokers, autonomic imbalance may be the best modifiable risk factor for interventions aimed at preventing metabolic syndrome and its consequent disorders.

To our knowledge, this is the first report of autonomic imbalance predicting the development of metabolic syndrome. As the relative newcomer among modifiable targets for public health interventions, HRV deserves more careful study. Several reports and reviews have explored the importance of HRV as a measure of autonomic imbalance in relationship to cardiac outcomes and early death (12,20). The list of interventions that can modify RHR and HRV is ample and includes exercise, β-blockers, biofeedback, selective serotonin reuptake inhibitors, relaxation training, and psychotherapy. Given that RHR and HRV are measureable, predictive, and modifiable, they deserve to be considered as targets for preventive clinical trials in patients at risk for diabetes, obesity, and heart disease. For example, clinical trials should focus on determining what the optimal interventions are for correcting autonomic imbalance, and at what point in the course of development of multiple metabolic risks it is best to intervene.

Several limitations of this analysis constrain the generalizability of the findings. The sample was white, middle aged, and mostly middle class, so our findings may not apply to other populations. We selected baseline measures of autonomic imbalance and do not yet know about the importance of the duration of autonomic imbalance for prediction of risk of metabolic syndrome. We recognize that we examined just two measures of HRV. The debate in the literature about which measures of HRV best reflect autonomic nervous system activity and dysregulation points to the need for more research on HRV measures as predictors of metabolic outcomes. Other variables for which we lacked reliable data, such as physical activity or insulin resistance, may influence the relationship between autonomic imbalance and metabolic syndrome. The surprising lack of contribution of depressive symptoms to risk for metabolic syndrome in any of the models raises a question about the sufficiency of the single Center for Epidemiologic Studies Depression Scale measure for capturing the metabolic impact of clinical depression. Our substitution of BMI for WC, given the lack of FHS data on WC during this period, may have contributed to an underestimation of the effect of the effect of autonomic imbalance on incident metabolic syndrome, according to Windham and colleagues (21).

Further research should focus on the relative effects of autonomic imbalance and other predictors on each of the five component conditions of metabolic syndrome and, most importantly, on incident metabolic disorders and mortality. The answers to these questions will clarify the pathways from autonomic imbalance to metabolic risks and metabolic disorders.

All authors contributed to the study design and to manuscript revisions. L. Wulsin is the guarantor of this publication. Data management was done by J. Massaro and P. Horn. Data analyses were done by P. Horn with contributions from L. Wulsin, J. Perry, and J. Massaro. L. Wulsin, P. Horn, J. Perry, and J. Massaro contributed to manuscript writing. We would also like to acknowledge the following people for their contributions and input: Robert Carney, PhD, Washington University; Robert M. Cohen, MD, University of Cincinnati; Neil Richant, MD, PhD, University of California at San Diego; Anil Menon, PhD, University of Cincinnati; James Herman, PhD, University of Cincinnati; and John Morrison, PhD, University of Cincinnati.

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REFERENCES


