Prospective Study of Phobic Anxiety and Risk of Coronary Heart Disease in Men

Ichiro Kawachi, MBChB; Graham A. Colditz, MBBS; Alberto Ascherio, MD; Eric B. Rimm, ScD; Edward Giovannucci, MD; Meir J. Stampfer, MD; Walter C. Willett, MD

Background To examine prospectively the association between self-reported symptoms of phobic anxiety and subsequent risk of coronary heart disease, a 2-year follow-up study was conducted of a cohort of 33 999 US male health professionals, aged 42 to 77 years in 1988, who were free of diagnosed cardiovascular disease at baseline. Levels of phobic anxiety were assessed using the Crown-Crisp index, a short, diagnostic self-rating scale used for common phobias. Main outcomes were incidents of coronary heart disease consisting of nonfatal myocardial infarction (MI) and fatal coronary heart disease (CHD).

Methods and Results One hundred sixty-eight incident cases of CHD occurred during 2 years of follow-up (128 cases of nonfatal MI and 40 cases of fatal CHD). The age-adjusted relative risk of fatal CHD among men with highest levels of phobic anxiety (scoring 4 or higher on the Crown-Crisp index) was 3.01 (95% confidence interval, 1.31 to 6.90) compared with men with the lowest levels of anxiety (scoring 0 or 1 on the phobia index). Risk of fatal CHD increased with levels of phobic anxiety ($P$ trend=.002). When fatal CHD was further categorized into sudden and nonsudden coronary death, the excess risk was confined to sudden death (relative risk among men scoring 3 or higher on the phobia index was 6.08; 95% confidence interval, 2.35 to 15.73). No association was found between phobic anxiety and risk of nonfatal MI. These findings remained essentially unchanged after adjusting for a broad range of cardiovascular risk factors.

Conclusions The specificity, strength, and dose-response gradient of the association, together with the consistency and biological plausibility of the experimental and epidemiologic evidence, support a strong causal association between phobic anxiety and fatal CHD. (Circulation. 1994;89:1992-1997.)

Key Words • anxiety • coronary heart disease • death, sudden

Several studies have suggested an increased risk of coronary heart disease (CHD) among patients with phobic anxiety, panic disorder, selection bias in the choice of clinic populations, or failure to distinguish between sudden and nonsudden coronary death. Panic disorder affects between 2% and 5% of the general population and 10% to 14% of patients in cardiology practice. The higher prevalence of panic disorder among patients attending cardiology clinics has been attributed partly to overlap between symptoms of panic and atypical chest pain. A recent report suggested an increased risk of fatal myocardial infarction (MI) among women using benzodiazepines, tricyclic antidepressants, and barbiturates. However, the study provided no details of the psychiatric conditions for which the drugs had been prescribed.

We prospectively examined the relation between phobic anxiety and the subsequent incidence of CHD (including sudden coronary death) in a cohort of US male health professionals. Phobic anxiety was assessed by the Crown-Crisp index, a short, clinical self-rating scale for common phobias such as fear of enclosed spaces, illness, going out alone, heights, and crowds.

Methods

The Health Professionals Follow-up Study is a longitudinal study of risk factors for cardiovascular disease and cancer among 51 529 US men aged 40 to 75 years in 1986. The study population consists of 29 683 dentists, 10 098 veterinarians, 4185 pharmacists, 3835 optometrists, 2218 osteopathic physicians, and 1600 podiatrists. The study began in 1986, when cohort members completed a mailed questionnaire on heart disease risk factors, medical history, and diet. Follow-up questionnaires are sent every 2 years to update this information.

Assessment of Phobia and Other Exposures

All participants in the study were asked to complete the phobic anxiety scale of the Crown-Crisp experiential index as part of the 1988 mailed questionnaire. These questions were included specifically to address the hypothesis that phobic anxiety is a risk factor for CHD. The index measures personality traits and symptoms of phobic anxiety and has been validated in psychiatric outpatients. It is a standardized, self-rating inventory of eight questions with two to three levels of possible responses to each question, allowing scores ranging from 0 to 16 (with higher scores given to higher levels of phobic anxiety). After a previous study that used the Crown-Crisp index, we categorized respondents into groups based on their item scores: 0 or 1 (reference category), 2, 3, and 4 or higher (highest levels of phobic anxiety).

In addition to the items on phobia, we obtained information from the 2-yearly questionnaires on the participants' medical history, current smoking habits, weight, height, levels of physical activity, alcohol intake, and parental history of MI, including the age of each parent at the first event.

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Assessment of Morbidity and Mortality

Fatal CHD (further classified into sudden death and non-sudden coronary death) and nonfatal MI occurring between the return of the 1988 questionnaire and January 31, 1990, were considered as end points for analysis. We wrote to participants who reported an incident MI on the 1990 questionnaire to confirm the report and to request permission to review medical records. A diagnosis of MI was confirmed if it met World Health Organization criteria—symptoms plus either typical ECG changes or elevated levels of cardiac enzymes. An MI was classified as "probable" if the medical records could not be obtained but the participant required hospital admission and the diagnosis was corroborated by supplementary correspondence or telephone interview.

Most deaths were reported by next of kin, work associates, or postal authorities. In addition, the National Death Index was used to identify deceased cohort members among persistent nonresponders to the questionnaire mailings. A death from an MI was confirmed from medical records or autopsy reports. Fatal coronary disease was considered confirmed if it was listed as the primary cause of death on the death certificate and if a diagnosis of incident coronary disease (after January 1, 1988) could be confirmed from hospital records or interviews from the next of kin. The cause of death on the death certificate was not sufficient by itself to confirm the diagnosis of CHD death. Sudden death was defined as death within 1 hour of the onset of symptoms when no previous serious illness was reported and no other plausible cause of death (other than coronary disease) was reported.

Because a prior diagnosis of cardiovascular disease might influence the responses to certain items on the Crown-Crisp index (eg, "Do you find yourself worrying about getting some incurable illness?"). we excluded from analyses all members of the cohort who reported a diagnosis of angina, MI, coronary artery bypass graft, or stroke before the return of their 1988 questionnaire (n=4651 men). In addition, we excluded 12879 men who answered a shorter questionnaire in 1988 that did not include the Crown-Crisp index. This left a total of 33999 men available for follow-up.

After repeated mailings to nonrespondents, including the use of certified mail, we obtained a 96% response rate to the 1990 questionnaire from the cohort.

Data Analysis

Each participant accumulated person-months of follow-up from the date of return of the 1988 questionnaire to January 31, 1990 (or for those who developed CHD or died, up to the date of the event). Incidence rates of CHD were age-adjusted using 5-year age groups. Relative risks (RRs) were adjusted for age as well as for multiple potential confounding variables using logistic regression analysis. The multivariate models included terms for age (in 5-year age categories), cigarette smoking (categorized as current smokers of 1 to 14, 15 to 24, or ≥25 cigarettes per day, past smokers, or never-smokers), alcohol intake (0.0, 0.01 to 4.9, 5.0 to 14.9, 15.0 to 24.9, 25.0 to 49.9, and ≥50.0 g/d), body mass index (deciles), history of hypertension, diabetes mellitus, hypercholesterolemia, family history of MI before the age of 60 years, and physical activity (tertiles). When appropriate, we performed the Mantel test for linear trend across levels of phobic anxiety and reported the two-tailed P values.

Results

The scores on the phobic anxiety index ranged from 0 to 10 (out of a possible maximum score of 16) in this population. We categorized men into the following groups: 0 or 1 (reference category, corresponding to the lowest levels of self-reported symptoms: 68.6% of the population), 2 (14.3%), 3 (10.3%), or 4 or more (6.8%). As noted in previous studies, the age-standardized prevalence of smoking increased with levels of phobic anxiety, although the overall prevalence of current smoking in this population was below 10% (Table 1). Men with phobic symptoms also more frequently reported a history of hypertension, hypercholesterolemia, and diabetes mellitus.

During 2 years of follow-up, 168 cohort members were diagnosed with incident CHD, consisting of 128 cases of nonfatal MI and 40 cases of fatal CHD (including 16 cases of sudden death and 24 of nonsudden coronary death). No association was found between phobic anxiety and RRs of nonfatal MI (P trend=.54) or total CHD (P trend=.56) (Table 2). However, there was a dose-response relation (P trend=.04) between the level of phobic anxiety and RR of fatal CHD. The multivariate RR of fatal CHD among men who scored 4 or higher on the phobia scale was 2.5 (95% confidence interval (CI), 1.00 to 5.96) compared with men who scored 0 or 1. The increased risk of fatal CHD was due
TABLE 2. Age-Adjusted and Multivariate Relative Risks of Fatal Coronary Heart Disease, Nonfatal Myocardial Infarction, and Total Coronary Heart Disease by Level of Phobic Anxiety

<table>
<thead>
<tr>
<th></th>
<th>Level of Phobic Anxiety*</th>
<th></th>
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<th></th>
<th>Test for Trend, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0, 1</td>
<td>2</td>
<td>3</td>
<td>≥4</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>41 722</td>
<td>8639</td>
<td>6205</td>
<td>4110</td>
<td></td>
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<tr>
<td>Fatal heart disease</td>
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<tr>
<td>Cases</td>
<td>19</td>
<td>5</td>
<td>9</td>
<td>7</td>
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<tr>
<td>Age-adjusted relative risk</td>
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<td>1.10</td>
<td>2.72</td>
<td>3.01</td>
<td>.002</td>
</tr>
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<td>0.41-2.93</td>
<td>1.27-5.81</td>
<td>1.31-6.90</td>
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<tr>
<td>Multivariate relative risk†</td>
<td>1.00</td>
<td>1.02</td>
<td>2.62</td>
<td>2.45</td>
<td>.04</td>
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<tr>
<td>Confidence interval</td>
<td>0.38-2.75</td>
<td>1.17-5.86</td>
<td>1.00-5.96</td>
<td></td>
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<tr>
<td>Nonfatal infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>84</td>
<td>23</td>
<td>12</td>
<td>9</td>
<td></td>
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<tr>
<td>Age-adjusted relative risk</td>
<td>1.00</td>
<td>1.23</td>
<td>0.88</td>
<td>1.00</td>
<td>.95</td>
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<td>Confidence interval</td>
<td>0.78-1.95</td>
<td>0.48-1.61</td>
<td>0.50-1.98</td>
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<td></td>
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<tr>
<td>Multivariate relative risk†</td>
<td>1.00</td>
<td>1.17</td>
<td>0.82</td>
<td>0.89</td>
<td>.54</td>
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<tr>
<td>Confidence interval</td>
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<td>0.44-1.50</td>
<td>0.45-1.79</td>
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<tr>
<td>Total coronary heart disease</td>
<td>103</td>
<td>28</td>
<td>21</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted relative risk</td>
<td>1.00</td>
<td>1.20</td>
<td>1.23</td>
<td>1.40</td>
<td>.13</td>
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<tr>
<td>Confidence interval</td>
<td>0.79-1.83</td>
<td>0.77-1.97</td>
<td>0.83-2.37</td>
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<tr>
<td>Multivariate relative risk†</td>
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<td>1.14</td>
<td>1.15</td>
<td>1.24</td>
<td>.56</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>0.75-1.73</td>
<td>0.71-1.84</td>
<td>0.73-2.11</td>
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</table>

*Scores on the Crown-Crisp phobia scale.
†Adjusted for age (5-year age categories), deciles of body mass index, smoking habit (never, past, and current in categories of 1 to 14, 15 to 24, and 25 or more cigarettes per day), history of hypertension, diabetes mellitus, hypercholesterolemia, parental history of myocardial infarction before age 60 years, daily alcohol intake (0, 0.01-4.9, 5.0-14.9, 15.0-24.9, 25.0-49.9, or ≥50 g/d), and tertiles of physical activity.

to an excess risk of sudden death (Table 3). The multivariate risk of sudden death among men scoring 3 or higher on the phobia index was 6.08 (95% CI, 2.35 to 15.73). Addition of regular aspirin use and vitamin E intake (in quintiles) to the multivariate models made little difference to the RR estimates.

Three individual items on the phobic anxiety index were associated with an elevated risk of fatal CHD (Table 4); “always feeling panicky in crowds” (RR, 10.8; 95% CI, 2.2 to 52.5); “worrying unduly when relatives are late coming home” (RR, 2.3; 95% CI, 1.2 to 4.2); and “definitely feeling more relaxed indoors” (RR, 3.7; 95% CI, 2.1 to 6.4).

To check the possibility that our findings were due to an adverse effect of drugs used to treat phobic anxiety, we examined the risks of CHD in the subgroup of men who were not using any regular medications in 1988. Within this subgroup, the RR of fatal CHD (based on four cases) among men who scored 3 or 4 on the index was 5.57 (95% CI, 1.01 to 30.90); and the RR of sudden death (based on three cases) was 11.27 (95% CI, 1.73 to 73.42). Our findings were therefore unlikely to be explained by an adverse effect of medication.

Finally, we repeated all the analyses without excluding men with diagnosed cardiovascular disease (angina, MI, coronary artery bypass graft, or stroke) at baseline. This more than doubled the number of available fatal CHD end points (from 40 to 95 cases). Compared with men with the lowest levels of phobic anxiety, the multivariate RR of fatal CHD were 1.8 (95% CI, 1.1 to 3.0) among men who scored 2, 1.9 (95% CI, 1.1 to 3.4) among men who scored 3, and 2.2 (95% CI, 1.2 to 4.0) among men who scored 4 or higher on the phobia index. The multivariate RR of sudden death were 1.6 (95% CI, 0.3 to 8.4) among men who scored 2, 7.7 (95% CI, 2.4 to 24.5) among men who scored 3, and 4.3 (95% CI, 1.0 to 18.5) among men who scored 4 or higher.

Discussion

Our prospective data show a strong association between phobic anxiety and fatal CHD, in particular, sudden death. The association could not be explained by confounding by smoking habit, alcohol intake, and a broad range of other cardiovascular risk factors. The specificity of the association with fatal CHD as well as the dose-response gradient are both consistent with the Northwick Park Heart study, which also used the Crown-Crisp index as the measure of phobic anxiety.1 In that prospective study, based on a population of 1457 healthy white men aged 40 to 64 years, the authors found a multivariate RR of fatal CHD of 2.54 (95% CI, 1.08 to 5.98) among men who scored 3 or 4 on the index, and an RR of 3.77 (95% CI, 1.64 to 8.64) among men who scored 5 or higher. As in the present study, no elevated risks were observed for nonfatal ischemic heart disease. On the other hand, the Northwick Park Heart
study did not distinguish between sudden coronary death and nonsudden fatal CHD. Our study suggests that the risk of phobic anxiety is specific to sudden coronary death.

A recent general practice–based, case-control study of fatal MI in British women aged 16 to 39 years found excess risks for use of benzodiazepines (OR, 3.7; 95% CI, 2.1 to 6.4), tricyclic antidepressants (OR, 2.7; 95% CI, 1.5 to 4.9), and barbiturates (OR, 12.0; 95% CI, 1.4 to 98).10 Although the authors acknowledged that use of psychotropic drugs may be a marker for panic disorder or phobic anxiety, no data on psychiatric history were provided. Both benzodiazepines and tricyclic antidepressants are effective treatments for panic disorder.15 While tricyclics can have effects on cardiac electrophysiology (especially prolongation of the QT interval, which may predispose to arrhythmia), benzodiazepines are free of adverse cardiac effects. The finding of similarly elevated risks of fatal MI for the two drugs suggests a common link with a condition leading to their prescription rather than a drug-associated adverse effect. Such an interpretation is supported by the finding in the present study of an elevated risk of fatal CHD within the subgroup of men receiving no medication.

Several other studies have also suggested an association between CHD and phobic anxiety or panic disorder.2-4 Weissman et al.4 reported a cross-sectional study among 5034 residents in New Haven, Conn, who were surveyed regarding lifetime diagnosis of panic disorder and self-reported prevalence of heart attack and stroke. An association was found between panic disorder and heart attack (OR adjusted for age, sex and socioeconomic status, 4.5; 95% CI, 1.7 to 12.3), as well as stroke (OR, 11.9; 95% CI, 4.2 to 33.8), although the self-reported diagnoses of cardiovascular events were not confirmed by independent medical review.

A 35-year follow-up study of male inpatients with panic disorder reported a standardized cardiovascular mortality ratio of 2.0 (P < .01) relative to age-, period-, and sex-matched general population.2 The diagnostic specificity of the association between panic disorder and CHD was apparent from the absence of excess risk among similarly followed cohorts with primary depression3 or obsessive-compulsive disorder.16 A potential limitation of the present study is that our cohort consists of male health care professionals, so our results may not be generalizable to the general population. About 80% of patients affected with phobic anxiety are women.5,6 Our group is currently investigating this association in two cohorts of over 200,000 women. Our study did not seek to obtain information on the clinical diagnosis of panic disorder. On the other hand, the instrument we used has been validated in psychiatric outpatients and used extensively in other studies.1,11,17-19 No information is available on the stability of Crown-Crisp index scores over time. However, the symptoms of phobic anxiety are generally known to begin in early adulthood, and the natural course of panic disorders tends to be chronic in nature.20 In the present study, higher levels of phobic anxiety were associated with higher self-reported prevalence of hypertension, high cholesterol, and diabetes (Table 1). It is possible that individuals’ responses to the phobic anxiety index were related to their knowledge and fears of accumulating risk factors for CHD. However, this fails to explain why an association was found between phobic anxiety and fatal CHD (particularly sudden coronary death) but not nonsudden MI.

The mechanisms by which phobic anxiety or panic disorder may cause fatal CHD include ventricular arrhythmia and hyperventilation leading to coronary artery spasm. Hyperventilation induced by anxiety is a well-recognized precipitant of coronary spasm21,22 that

<table>
<thead>
<tr>
<th>Level of Phobic Anxiety*</th>
<th>0, 1</th>
<th>2</th>
<th>3</th>
<th>≥4</th>
<th>Test for Trend, P</th>
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</thead>
<tbody>
<tr>
<td>Sudden coronary death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted relative risk</td>
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<td>1.70</td>
<td>8.01</td>
<td>3.24</td>
<td>.002</td>
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<tr>
<td>Confidence interval</td>
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<td>3.07-20.93</td>
<td>0.69-15.26</td>
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<td>Multivariate relative risk†</td>
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<td>1.65</td>
<td>8.43</td>
<td>3.11</td>
<td>.01</td>
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<td>Confidence interval</td>
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<td>0.58-16.55</td>
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<tr>
<td>Nonsudden coronary death</td>
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<tr>
<td>Cases</td>
<td>14</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted relative risk</td>
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<td>0.88</td>
<td>0.82</td>
<td>2.93</td>
<td>.14</td>
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<td>Confidence interval</td>
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<td>0.19-3.60</td>
<td>1.10-7.82</td>
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<td>0.79</td>
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<tr>
<td>Confidence interval</td>
<td>0.23-2.89</td>
<td>0.18-3.51</td>
<td>0.81-6.71</td>
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<td></td>
</tr>
</tbody>
</table>

*Scores on the Crown-Crisp phobia scale.
†Adjusted for age (5-year age categories), deciles of body mass index, smoking habit (never, past, and current in categories of 1 to 14, 15 to 24, and 25 or more cigarettes per day), history of hypertension, diabetes mellitus, hypercholesterolemia, parental history of myocardial infarction before age 60 years, daily alcohol intake (0, 0.01-4.9, 5.0-14.9, 15.0-24.9, 25.0-49.9, or ≥50 or more g/d), and tertiles of physical activity.

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can subsequently induce chest pain, ventricular arrhythmias, and MI.\textsuperscript{23} In a series of experimental and clinical studies, Lown and others\textsuperscript{24-29} established three factors leading to fatal ventricular arrhythmias: first, the presence of myocardial electrical instability; second, operation of an intense psychological state burdening daily life; and third, a proximate charged psychological event that may trigger the arrhythmia. Among 117 patients with life-threatening ventricular arrhythmias,\textsuperscript{29} the most common underlying psychological states were either affective depression or a sense of emotional entrapment without an exit. A psychological trigger for arrhythmia was identified in 21\% of these patients and usually preceded the arrhythmia by less than 1 hour.

In summary, we have shown that apparently well men at higher risk of sudden death can be identified by a series of simple, self-administered questions. The specificity of the association between phobic anxiety and fatal CHD, the consistency and biological plausibility of the experimental, clinical, and epidemiological evidence, as well as the strength and dose-response gradient of the association together suggest a causal relation of phobia to fatal CHD, particularly sudden death.

**Acknowledgments**

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