INTRODUCTION
Prevalence of hypertension and diabetes increases with age (1-3), while total cholesterol levels and body mass index often decline in the elderly (4-10). In light of the importance of age on increasing the risk of coronary heart disease (CHD) (11), these age-related trends suggest a changing role for total cholesterol and body mass index in the development of CHD in older individuals and an increased role for hypertension and diabetes. Such possibilities, however, have not been fully explored, but if true, documenting age-related changes in risk factor effects could improve strategies for targeting those factors that have the greatest effect on CHD risk in the elderly. The purpose of this report is to examine the relation between age and common risk factors for CHD and to describe the way in which risk factor effects can change over a broad range of ages from middle adulthood to late-life in men enrolled in the Honolulu Heart Program.

METHODS
From 1965 to 1968, the Honolulu Heart Program began following 8006 men of Japanese ancestry living on the island of Oahu, Hawaii for the development of CHD and stroke (12, 13). At the time of study enrollment, participants received a complete physical examination when they were aged 45 to 68 years. Procedures were in accordance with institutional guidelines and approved by an institutional review committee. Informed consent was obtained from the study participants.

Information on cardiovascular events that occurred after the baseline examination was obtained through a compre-
hensive system of surveillance of hospital discharges, death certificates, autopsy records, and at repeat examinations given in the course of follow-up. For this report, subjects were followed for the first occurrence of CHD. Here, CHD is defined to include unequivocal findings of nonfatal myocardial infarction, coronary death, and sudden death within an hour that could not be attributed to another cause. Identification of such events was confirmed by a review of all suspected coronary outcomes by the Honolulu Heart Program Morbidity and Mortality Review Committee. After excluding 325 men with prevalent CHD (including angina pectoris and coronary insufficiency) at the time of study enrollment, 7681 remained for follow-up. Further description of the definition of CHD is provided elsewhere (13).

Risk factor information that was updated during the course of follow-up included hypertensive status, total cholesterol level, diabetes, body mass index (kg/m²), cigarette smoking status, alcohol intake, and physical activity. To assess the effects of a risk factor on the incidence of CHD, proportional hazards regression models were used (14). While such models allow for the adjustment of other factors, they also allow for the effect of a risk factor to vary with time as they become updated with age. Risk factors were also compared across 10-year age ranges based on standard ANCOVA methods (15). All reported p-values were based on 2-sided tests of significance.

Measurement of the risk factors were made at the time of study enrollment (1965 to 1968), with updates occurring at 6 (1971 to 1974), 15 (1980 to 1982), and 26 (1991 to 1993) years into follow-up. Approximately 90 and 80% of the surviving members of the original Honolulu Heart Program cohort participated in the 6th and 26th year anniversary examinations, respectively. The examinations that occurred 15 years into follow-up included a random sample of men who were selected to participate in the Cooperative Lipoprotein Phenotyping Study (16).

To establish uniform and non-overlapping follow-up periods after each risk factor measurement, four 6-year intervals of follow-up for CHD were created. Follow-up was restricted to men who were free of known CHD at the beginning of each period (including angina pectoris and coronary insufficiency). With each risk factor modeled as a time-varying covariate, subjects could contribute up to four 6-year person intervals. The intervals of follow-up were also pooled to enable calculation of 6-year incidence rates of CHD according to an updated age. This further allowed for the calculation of incidence rates across a broad range of ages from 45 to 93 years as age was updated from the time of study enrollment (1965 to 1968) to the examination that occurred 26 years later (1991 to 1993). Such pooling also permitted an assessment of risk factor effects on CHD as they might change with increasing age. Here, cross-product terms between a risk factor and age were modeled. Tests for interaction between a risk factor and age on the risk of CHD as both variables were updated with time were then based on the estimated regression coefficients and standard errors that were associated with these terms.

Among the risk factors considered in this report, hypertension was defined as a systolic or diastolic blood pressure ≥ 160 and 90 mm Hg, respectively, or based on the use of antihypertensive medication. To be considered normotensive, systolic and diastolic blood pressures needed to be < 140 and 90 mm Hg, respectively. Men who were neither normotensive nor hypertensive were classified as having borderline hypertension. Study participants were also classified as having diabetes on the basis of a medical history (physician diagnosed or based on the reported use of insulin or the receipt of oral hypoglycemic therapy).

Assessment of overall metabolic output during a typical 24-hour period was based on the use of a physical activity index. The physical activity index was derived by summing the average number of hours per day spent in five different activity levels (basal, sedentary, slight, moderate, and heavy) after each was multiplied by a weighting factor that corresponded to the level of exertion needed to undertake the activity. High levels of the physical activity index indicate active lifestyles, and low levels indicate inactive lifestyles (17–20). The physical activity index was derived at all examinations except the examination that occurred 6 years into follow-up (1971 to 1974). Removing physical activity in this report does not change the reported associations that were observed between the other factors and the risk of CHD. High-density lipoprotein cholesterol, serum glucose, triglycerides, and other risk factors were not examined since they were measured too infrequently during the course of follow-up to enable an assessment of their effects across a broad range of ages. Further description of the risk factors is provided elsewhere (21–23).

### RESULTS

Among the 7681 men free of CHD at the time of study enrollment, 18,456 person intervals were available for follow-up to a coronary event. The overall average age at the beginning of follow-up was 61 ± 10 years (range: 45–93). Across the combined 6-year person intervals, 677 men developed CHD (3.7% in 18,456 person intervals). The average time to an event was 3.0 ± 1.6 years (range: 0.1–6). For men aged 45 to 54 years, the 6-year incidence of CHD was 1.8% (Table 1). Incidence increased consistently with age to 8.1% in those who were 75 years and older (p < 0.001).

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**Selected Abbreviation**

CHD = coronary heart disease
TABLE 1. Six-year percent incidence of CHD according to age

<table>
<thead>
<tr>
<th>Age</th>
<th>6-year person intervals at risk</th>
<th>Number of events</th>
<th>Incidence* of CHD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>5,465</td>
<td>101</td>
<td>1.8</td>
</tr>
<tr>
<td>55–64</td>
<td>7,089</td>
<td>217</td>
<td>3.1</td>
</tr>
<tr>
<td>65–74</td>
<td>3,483</td>
<td>164</td>
<td>4.7</td>
</tr>
<tr>
<td>75–93</td>
<td>2,419</td>
<td>195</td>
<td>8.1</td>
</tr>
<tr>
<td>Overall</td>
<td>18,456</td>
<td>677</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*Incidence of CHD increases significantly with advancing age (p < 0.001).

As might be expected, significant changes were observed in the risk factor levels as age increased (Table 2). The largest changes seemed to occur for the percent of men who were hypertensive and who smoked cigarettes when follow-up began. For those aged 45 to 54 years, 20.9% were hypertensive, while in the oldest group of men, the percent was more than doubled (53.3%, p < 0.001). While hypertension increased with age, the percent who smoked cigarettes declined from 47.9% in the youngest age range to 7.4% in those who were the oldest (p < 0.001). Frequency of diabetes increased with age (p < 0.001), although the greatest increase occurred after age 54. Risk factors that declined with age included total cholesterol, body mass index, alcohol intake, and the physical activity index. The latter changes occurred uniformly with advancing age (p < 0.001).

Among the risk factors, relations with incident CHD often varied with age (Fig. 1, Fig. 2). Although the risk of CHD increased with increasing hypertension severity, associations were weakest in the oldest age range (Fig. 1). While hypertension continued to be associated with an excess risk of CHD, this latter finding is largely due to a jump in CHD risk that was observed in the oldest men (75 to 93) who were normal or borderline hypertensive.

Similar findings were also observed for total cholesterol (Fig. 1). Unlike hypertension, however, the positive association between total cholesterol and CHD in men <75 was no longer statistically significant in those who were older. As with men who were normal or borderline hypertensive, men with desirable cholesterol concentrations (<200 mg/dl) experienced a large increase in CHD risk after age 74 years.

In contrast, the effect of diabetes on CHD risk was similar across age ranges. Regardless of age, men with diabetes had a consistent 2-fold excess risk of CHD vs. men without diabetes. Associations between body mass index and CHD appeared to reverse with advancing age. Positive associations were strong in the younger age ranges (45 to 64), but became negligible in men aged 65 to 74 years. A significant inverse relation emerged in men aged 75 years and older (p < 0.01).

Although it appears that the association between cigarette smoking and CHD declines with age (Fig. 2), this could be a consequence of limited statistical power through reductions in the percent of men who continued to smoke as they became older (Table 2). In addition, for those who continued to smoke, the average number of cigarettes smoked per day declined from 28 in men aged 45 to 54 years to 14 in those 75 and older (p < 0.001). While the number of cigarettes smoked per day was positively related to the risk of CHD (p < 0.001), interactions with age were not statistically significant, and within age group effects seemed weaker than they were for the simple comparison between smokers and non smokers. Combined with reductions in the frequency of smoking and the fewer cigarettes smoked per day that occurred with increasing age, exposure to smoking in this elderly sample may have been sufficiently reduced to where its contribution to the risk of CHD became minor relative to other risk factors.

The protective effect of alcohol on CHD risk also declined with advancing age while use of alcohol was at its highest in the oldest age range (Table 2). In contrast, based on a comparison of tertiles of the physical activity index, an inverse association between physical activity and CHD appeared strongest in the oldest age range (p < 0.001). Risk of CHD was highest in the oldest (75 to 93) and most sedentary men.

Estimated relative risks of disease (Fig. 3, Fig. 4) were also calculated according to the presence vs. absence of a risk factor by 10-year age strata after adjustment for the other risk factors in Table 2. Tests for changing risk factor effects with advancing age are also given; i.e., a test for interaction.

As previously noted in Figure 1, the diminished association between hypertension and CHD with advancing age was statistically significant (p = 0.013). The relative risk of CHD in hypertensive vs. normotensive men declined consistently from 3.7 in those aged 45 to 54 years to 1.7 in those aged 75 years and older (Fig. 3).

In contrast, the diminished association between total cholesterol and CHD with advancing age that was noted earlier in Figure 1 is no longer statistically significant after risk factor adjustment (p = 0.125). Nevertheless, the relative risk of CHD between men with total cholesterol levels at 240

TABLE 2. Average cardiovascular risk factors according to age

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>45–54</th>
<th>55–64</th>
<th>65–74</th>
<th>75–93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline (%)</td>
<td>17.3</td>
<td>18.2</td>
<td>20.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Hypertensive (%)</td>
<td>20.9</td>
<td>30.5</td>
<td>42.6</td>
<td>53.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>219</td>
<td>216</td>
<td>207</td>
<td>190</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8.6</td>
<td>13.1</td>
<td>15.0</td>
<td>12.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.1</td>
<td>23.7</td>
<td>23.4</td>
<td>23.1</td>
</tr>
<tr>
<td>Cigarette smoker (%)</td>
<td>47.9</td>
<td>38.2</td>
<td>23.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Alcohol drinker (%)</td>
<td>68.1</td>
<td>66.7</td>
<td>62.0</td>
<td>57.1</td>
</tr>
<tr>
<td>Physical activity index (%)</td>
<td>32.9</td>
<td>32.6</td>
<td>31.6</td>
<td>30.5</td>
</tr>
</tbody>
</table>

*Significant increase with advancing age (p < 0.001).
*Significant decline with advancing age (p < 0.001).
vs. 200 mg/dl was significant in men under age 65 years but not in those who were older (Fig. 3). Unlike total cholesterol, the positive association between body mass index and CHD in men <65 years of age became significantly diminished with advancing age ($p < 0.001$). Age had no effect on the association between diabetes and CHD ($p = 0.673$).

Among the other risk factors, effects of cigarette smoking (Fig. 4) on CHD declined with age ($p = 0.047$), while for men $\geq 55$ years, the protective effect of alcohol on CHD became less apparent in those aged $\geq 75$ years ($p < 0.001$). Although interaction effects with age were not statistically significant, the benefits from being physically active appeared strongest in the oldest men (75–93) vs. those who were younger. For the risk factors considered in this report, tests for nonlinear age-related effects on the incidence of CHD were not statistically significant.

**DISCUSSION**

Little is known about age-related changes in risk factor effects on the incidence of CHD. For hypertension, effects on morbidity and mortality become increasingly complex with advancing age (24). Some studies have shown an inverse relation between blood pressure and mortality in the elderly, while others have suggested relations that are U- or J-
shaped (25–30). Although findings from the Honolulu Heart Program indicate that the effect of hypertension on the risk of CHD is reduced in the elderly, results also suggest that the observed weakening is not necessarily a consequence of a decline in the importance in treating hypertension, but rather in the increased role that age has on promoting CHD in men without hypertension. The diminished association between hypertension and CHD with advancing age ($p < 0.013$) (Fig. 3) is equivalent to the observation that the effect of age on increasing the risk of CHD is not as strong in hypertensive men as it is in those who are normotensive (Fig. 1).

While absolute differences in the risk of CHD between age groups in Figure 1 look similar across hypertension strata, risk of CHD in normotensive men 54 years and younger increased 5.6-fold in those who were 75 and older. In hypertensive men, there was a 2.2-fold increased risk between these age groups. In comparison, relative increases (as opposed to absolute differences) in the risk of CHD with age were similar for men with and without diabetes (Fig. 1), resulting in the rather constant appearing relative risks that are shown in Figure 3. Here, the interaction between age and diabetes is not significant ($p = 0.673$).
Similar age-related changes seem to occur for total cholesterol as well, although the apparent decline in the association between total cholesterol and CHD with advancing age was not statistically significant. Unlike hypertension, total cholesterol was not significantly related to CHD in the oldest age range of men (75 to 93).

Past findings from the Honolulu Heart Program also suggest that current levels of total cholesterol in elderly men may poorly identify the coronary risk candidate (31). In addition, identifying borderline-high and high levels of total cholesterol based on concentrations that are observed in the elderly could leave the false impression that total cholesterol levels classified as desirable (<200 mg/dl) are associated with a healthy risk profile. This may not be the case if there has been a history of elevated total cholesterol levels (31). Similar data also appear elsewhere. In the Finnish Cohorts of the Seven Countries Study, greater than average losses in total cholesterol levels were associated with an increased risk of death from coronary heart disease, cardiovascular disease, and all-cause mortality over 15 years of follow-up in men aged 65 years and older (32).

The possibility that elevated cholesterol in younger years may have a carry-over effect through atherosclerotic damage that is resistant to change in spite of improvements in late-life lipid profiles is also consistent with observations from the Framingham Study (7). Here, percent carotid

*Test for interaction
stenosis in a sample of men whose average age was 75 years had a markedly reduced association with late-life cholesterol levels as compared with cholesterol levels measured earlier. Others have also described a weak relation between elevated total cholesterol levels in late life and the risk of coronary heart disease (33, 34), while arguments have also been made for closer clinical judgement in interpreting screening results in the elderly (35).

In contrast, the effect of diabetes on the risk of CHD remained constant across age ranges, while the effect of body mass index seemed to reverse from the youngest (45 to 54) to the oldest (75 to 93). Others have suggested a near inverse relation between body mass index and mortality in men aged 65 and older (36).

For the remaining risk factors, findings support ongoing efforts to encourage active life-styles across all ages. In middle-adulthood, physical activity may be especially important since it could effect the capacity to remain active in old age where an active lifestyle may have its greatest impact on preventing or delaying disease onset. The reduced burden from cigarette smoking on the risk of CHD that was observed in the elderly sample in Hawaii may also be a consequence of the promising benefits of smoking cessation that occurred earlier in life. Whether light alcohol con-
Assumption is associated with a reduced risk of CHD in the elderly deserves further study. Consumption of alcohol in older individuals could have a stronger association with poor nutrition, losses in body mass, and other adverse health behaviors than in adults who are younger. Assessment of the association between alcohol intake in the elderly and the risk of CHD is currently in progress in the Honolulu Heart Program.

Although hypertension, total cholesterol, and body mass index are primary risk factors for CHD, results from the Honolulu Heart Program indicate that relations between these factors and CHD become increasingly complex with advancing age. Clarification of the nature of these relations warrants further study. It may be that unmeasured factors associated with lipid metabolism, clotting, inflammation, immune response, and sex hormone secretion have an increasing independent effect on the risk of CHD in older individuals. Such a possibility, along with observations from the Honolulu Heart Program, suggests a need for updated strategies for the prevention of CHD as aging occurs.

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