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IS THE SERUM CHOLESTEROL-CORONARY HEART-DISEASE RELATIONSHIP MODIFIED BY ACTIVITY LEVEL IN OLDER PERSONS
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Is the Serum Cholesterol-Coronary Heart Disease Relationship Modified by Activity Level in Older Persons?

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Although coronary heart disease remains a leading cause of death and disability in old age, the relationship of serum cholesterol level to risk of coronary heart disease in old age is controversial. Data for 2,388 white persons aged 65–74 who participated in the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study (NHEFS) were examined to determine the relationship of serum cholesterol level to coronary heart disease incidence and whether activity level would modify this relationship.

While there was no overall relationship between serum cholesterol level and coronary heart disease risk in either men or women, the relationship between serum cholesterol level and coronary heart disease differed within activity groups. For persons who were more active, serum cholesterol level was associated with a graded increase in risk of coronary heart disease, from 1.3 (95% CI 0.7,2.3) in those with serum cholesterol level of 4.7–5.1 to 1.7 in those with serum cholesterol level of 6.2 mmol/L or more (95% CI 1.0,2.7), when compared with those with serum cholesterol level below 4.7. For the least active persons, all levels of cholesterol were associated with a significant inverse relative risk, including cholesterol of 6.2 mmol/L or more (Relative risk = 0.4 (95% CI 0.2,0.7)).

These data suggest that factors such as activity level may modify the serum cholesterol-coronary heart disease association in old age. The serum cholesterol-coronary heart disease association in more active older persons resembles that seen in younger populations, whereas the association in less active persons is that of serum cholesterol level and risk of cancer or death. The modification of the serum cholesterol-coronary heart disease association by activity level may have implications for appropriate clinical management as well as appropriate design of research studies of this association. J Am Geriatr Soc 39:747–754, 1991

The controversy regarding screening of older persons for serum cholesterol[1–4] has important public health consequences. Coronary heart disease remains the leading cause of death in old age and a major contributor to medical utilization and disability,[5] yet cholesterol prevalence data suggest that the cost of screening and treatment of high cholesterol could be substantial among older persons.[6] There is a paucity of knowledge on serum cholesterol level as a coronary heart disease risk factor in old age.[1] The association of serum cholesterol level with coronary heart disease may attenuate with age,[7–9] although a few studies have found relative risks in older persons within a range comparable to those in younger populations.[10–12] Multiple explanations have been suggested for the decline in relative risk with age[13] including a cholesterol-lowering effect of poor health. Drop in serum cholesterol has been associated with increased risk of coronary heart disease mortality in older persons.[14,15] Low serum cholesterol has been associated with other poor health outcomes including increased risk of mortality,[16,17] cancer,[18–20] and hemorrhagic stroke.[21]

Despite an apparent link between low cholesterol

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level and these poor health outcomes, factors which might modify the serum cholesterol-coronary heart disease relationship in old age have not been investigated. This may be particularly important for an older population where the proportion of persons with poor health increases with advancing age. To address this issue, we investigated the serum cholesterol-coronary heart disease association for 2,388 white persons aged 65–74 who participated in the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Followup Study (NHEFS). We were interested in two questions: Was serum cholesterol level associated with risk of coronary heart disease in this group of older persons, and did activity level modify the association of serum cholesterol level and coronary heart disease?

METHODS

Study Population The study population was drawn from the Epidemiologic Followup Study of the first National Health and Nutrition Examination Survey. The National Health and Nutrition Examination Survey I was conducted from 1971–1975 and involved extensive interviews and examinations of a representative sample of non-institutionalized Americans aged 1 to 74.[22] Followup information on these persons was obtained in two re-interview cycles in 1982–1984 and in 1986.[23,24] By 1986, fewer than 2 percent over age 65 were lost to followup. Death certificates have been obtained for the 97.5 percent of the 1,554 persons over age 65 at baseline who have died.

For this paper, the study population was the 3,179 white persons aged 65–74 who participated in the examination portion of that survey. We excluded from analysis those missing baseline serum cholesterol values and other covariate information ($n = 149$), those without a death certificate or a followup questionnaire ($n = 81$), and prevalent cases of coronary heart diseases at baseline, defined as those with history of a heart attack, heart failure, or history of taking medication for the heart ($n = 561$). The study was restricted to whites as the number of persons in the other race categories was too small to allow sufficient power to assess potential interactions. These exclusions resulted in a final study population of 2,388 persons, 1,095 men and 1,293 women. Mean followup for survivors was 12.9 years.

Outcome Incident cases of coronary heart disease were defined by a diagnosis of coronary heart disease (ICD-9 codes of 410-414) on hospital discharge records or by any mention of coronary heart disease on a death certificate (ICD-9 codes 410–414). This resulted in 414 incident events among men and 401 among women.

Risk Factors In NHANES I, serum cholesterol was measured at the CDC Laboratory by a semi-automated method based on that of Abell et al[25]; comparison of the CDC method with that of Abell led to an adjustment of 4.5 percent for bloods processed in 1971–1974.[26] For this paper, four levels of serum cholesterol were considered: 6.2 mmol/L or more (240 mg/dl), 5.2–6.1 (200–239), based on guidelines from the National Cholesterol Education Program,[27] 4.7–5.1 (180–199), and <4.7 mmol/L (<180 mg/dL) for low serum cholesterol values, consistent with the MRFIT analysis of continuous and graded cholesterol risk.[8] Covariates in multivariate models included baseline measures of coronary heart disease risk factors: age, body mass index (from measured weight and height at baseline (kg/m^2), analyzed in sex-specific quartiles), cigarette smoking (defined as current, former, and never smokers),[28] and having been told of diabetes by a physician. Systolic blood pressure was defined by four levels: <120, 120–139, 140–159, and 160 mmHg or more. No information was available on drug use other than the disease for which drugs were taken.

Level of usual and recreational activity was used for the activity level variable as this variable encompasses some aspects of physical functioning, and was one of the few such variables available for the entire population. Two questions on activity were included in the baseline health interview, "In your usual day, aside from recreation, how active are you?" and "Do you get much exercise in things you do for recreation?" Those "quite inactive" on usual activity and having "little or no exercise" on recreational activity were considered the low activity group (112 men, 130 women). Those "very active" on usual activity or "much exercise" on recreational, were considered to be the high activity group (451 men, 438 women); all others were considered to have moderate activity status (532 men, 725 women).

Statistical Methods The relationship of risk factors to serum cholesterol level was tested by likelihood ratio chi-squares. Incidence rates were calculated as per 1,000 person-years of followup. Cox proportional hazards models[29] were used to calculate relative risks and 95 percent confidence intervals relating risk factors to coronary heart disease incidence. All models were initially calculated separately for men and women; to increase power within activity strata, a final set of models was recalculated for both sexes by activity level with the addition to the model of a variable for gender. No interaction terms for sex and serum cholesterol level were significant, either overall or within activity level.

Sensitivity of the results to misclassification of outcome was tested by two strategies: first, since problems have been reported with the validity of death certificate diagnoses for older persons,[30] the 188 cases based only on death certificate information were excluded. In a second analysis, the 86 persons with self-report of

incident coronary heart disease (without hospital discharge or death record confirmation) were considered as cases. Both results are reported in an appendix.

Since this analysis is restricted to the elderly, only oversampling related to poverty areas could affect the results; poverty residence was therefore added to the final model, but results did not differ from the results presented in the paper.

RESULTS

The baseline distribution of standard cardiovascular risk factors in the study population is shown in Table 1. Quartile cutoffs for body mass index were similar for men and women except for the 4th quartile where women were heavier. Less than 10 percent of men and women had been told of diabetes by a physician. Thirty percent of the men and 14 percent of the women smoked at baseline. Twenty-nine percent of the men had systolic blood pressure of 160 mmHg or more compared with 36 percent of the women. About 34 percent of the men and 58 percent of the women had a serum cholesterol level of 6.2 mmol/L or greater; 13 percent of the men and 6 percent of the women had a serum cholesterol level of less than 4.7 mmol/L. About 10 percent of either sex was in the low activity group; 41 percent of the men reported high activity compared with 34 percent of the women.

Risk factors were examined in relation to level of serum cholesterol (Table 2). For both men and women, there appeared to be little relationship between serum cholesterol level and cigarette smoking or diabetes. Among women, those with body mass index in the lowest quartile were more likely to have lower serum cholesterol levels and heavier women were likely to have higher levels of serum cholesterol ($P = 0.03$); men in the lowest quartile also showed lower cholesterol levels. Systolic blood pressure and serum cholesterol distributions were related in men ($P = 0.03$) whereas blood pressure had little relation to serum cholesterol level in women ($P = 0.52$). Serum cholesterol varied with activity level for both men and women ($P = 0.08$ and $P = 0.0001$, respectively) with those with low activity more likely to have low serum cholesterol levels.

TABLE 1. DISTRIBUTION OF CORONARY HEART DISEASE RISK FACTORS BY SEX

Risk Factor	Men (n = 1,095)	Women (n = 1,293)
	kg/m^2	
Body mass index		
Quartile 1	<22.95	<22.85
Quartile 2	22.95–25.50	22.85–25.80
Quartile 3	25.51–27.68	25.81–29.18
Quartile 4	>27.68	>29.18
	Percent	
Diabetic (told by MD)		
Yes	8	9
No	92	91
Cigarette smoking		
Current	30	14
Former	34	10
Never	36	76
Systolic blood pressure (mmHg)		
Less than 120	10	5
120–139	28	26
140–159	33	33
160 or greater	29	36
Cholesterol (mmol/L)		
Less than 4.7	13	6
4.7–5.1	15	6
5.2–6.1	38	30
6.2 or greater	34	58
Activity level		
Higher	41	34
Moderate	49	56
Lower	10	10

Relationship of Serum Cholesterol Level to Coronary Heart Disease Incidence

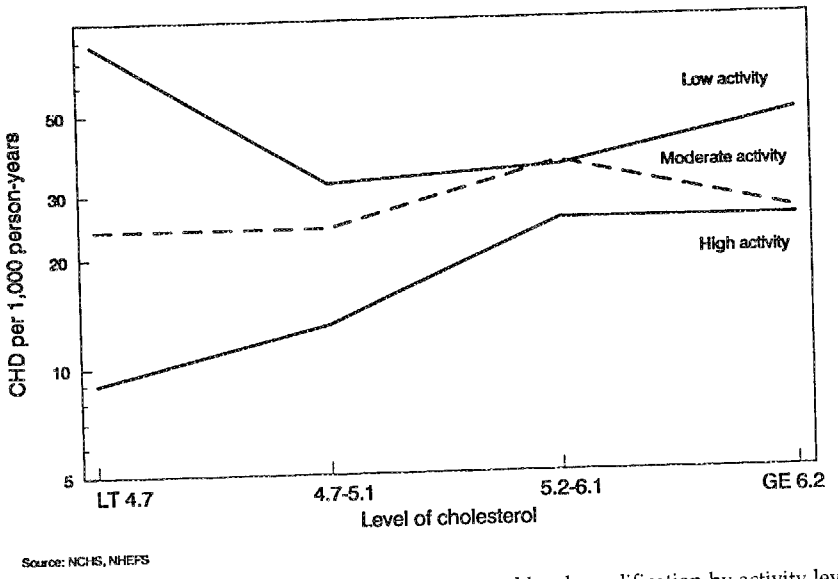
White Women Aged 65–74 at Baseline Women in the low activity group showed the highest rates of coronary heart disease at each level of serum cholesterol except for serum cholesterol of 5.2–6.1 (Figure 1), and differences in rates among activity groups was greatest for those with the lowest serum cholesterol levels.

Overall, there was no association of serum cholesterol level to coronary heart disease in women. However, relative risk estimates of serum cholesterol for coronary heart disease differed markedly within activity levels (Table 3). For women of high activity, those with serum cholesterol level of 6.2 or more had a risk estimate of 3.1 with a 95% confidence interval of 0.8 to 12.8. In women of moderate activity, risk estimates for serum cholesterol level were all elevated relative to those with serum cholesterol levels of less than 4.7, but only the 5.2–6.1 group showed substantial risk. Among women with low activity, all adjusted relative risk estimates for serum cholesterol level were less than 1 in comparison with those with a serum cholesterol level less than 4.7. An interaction term for activity level and serum cholesterol level was marginally significant, $P = 0.06$. The direction of these results was not substantially altered by considering "self-report only" cases as cases of coronary heart disease or by exclusion of those with only death certificate case status (Appendix A).

White Men Aged 65–74 at Baseline Men with lowest activity levels showed the highest incidence rates at each level of serum cholesterol level (Figure 2), with the greatest divergence in rates by activity level for those with the lowest serum cholesterol levels. As with women, the overall relative risk estimates did not

TABLE 2. DISTRIBUTION OF SERUM CHOLESTEROL LEVEL BY CORONARY HEART DISEASE RISK FACTORS AND SEX

Risk Factor	Sex and Serum Cholesterol Level (mmol/L)					
	Men			Women		
	<4.7	4.7–6.1	≥6.2	<4.7	4.7–6.1	≥6.2
	Percent			Percent		
Body mass index						
1st Quartile	18	52	30	9	41	50
2nd Quartile	12	51	37	6	35	59
3rd Quartile	11	55	34	3	37	60
4th Quartile	12	54	34	5	32	63
Diabetic (told by MD)						
Yes	15	49	36	9	43	48
No	13	53	34	5	36	59
Cigarette smoking						
Current	13	53	34	6	39	55
Former	12	56	32	4	40	56
Never	14	51	35	5	36	59
Systolic blood pressure (mmHg)						
Less than 120	18	50	32	4	44	52
120–139	11	50	39	6	39	55
140–159	13	58	29	5	34	61
160 or greater	13	52	35	6	36	58
Activity level						
Higher	12	55	33	4	34	62
Moderate	12	54	34	6	37	57
Lower	22	45	33	12	38	50



Source: NCHS, NHEFS

FIGURE 1. Coronary heart disease incidence rates by serum cholesterol level, modification by activity level in older women.

support a serum cholesterol-coronary heart disease association but did differ within activity strata. For men in the high activity group, there was a 50 percent excess risk of coronary heart disease for those with serum cholesterol level of 6.2 or more compared to those with serum cholesterol level below 4.7 (Table 4). Those of moderate activity status showed risks similar to the high activity group. For the low activity group, all adjusted relative risk estimates for serum cholesterol level were inverse in comparison with those with serum cholesterol level below 4.7. An interaction term for activity level and serum cholesterol level was marginally significant, $P = 0.08$. Results from these models were not substantially altered by changing the case status or exclusion of cases based on death certificate only information (Appendix A).

Analyses by Activity Level for Men and Women Combined As the modification of the serum cholesterol-coronary heart disease association by activity

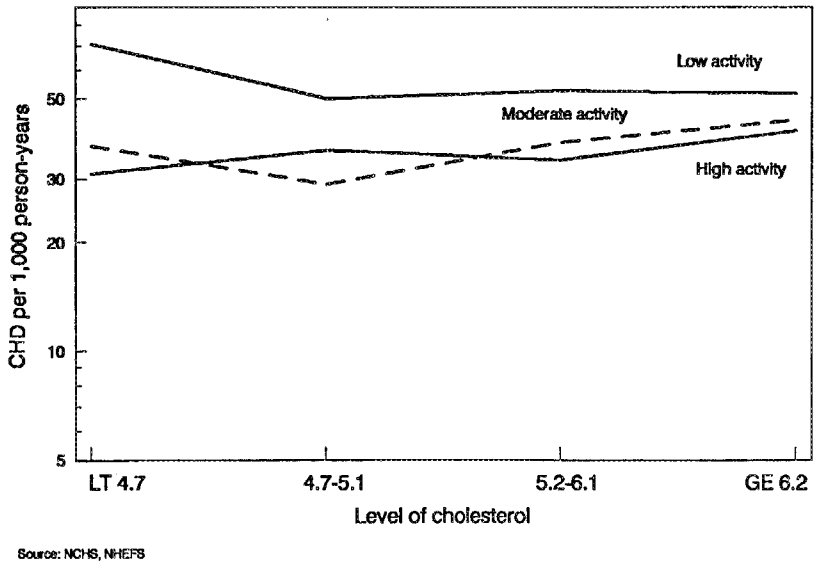


FIGURE 2. Coronary heart disease incidence rates by serum cholesterol level, modification by activity level in older men.

TABLE 3. CORONARY HEART DISEASE INCIDENCE IN RELATION TO ACTIVITY STRATA AND SERUM CHOLESTEROL LEVEL AMONG WOMEN

Activity Strata and Serum Cholesterol Level (mmol/L)	*n*	Cases	Incidence per 1,000 Person Years	Relative Risk and 95% Confidence Interval
All activity levels*				
Less than 4.7	72	19	26.4	1.0
4.7–5.1	80	19	21.4	0.8 (0.4,1.6)
5.2–6.1	392	134	31.8	1.3 (0.9,2.2)
6.2 or greater	749	229	27.4	1.1 (0.7,1.8)
Stratified by activity**				
Higher activity				
Less than 4.7	17	2	9.3	1.0
4.7–5.1	24	4	12.9	1.4 (0.3,7.9)
5.2–6.1	126	35	24.5	3.6 (0.9,15.1)
6.2 or greater	271	77	24.8	3.1 (0.8,12.8)
Moderate activity				
Less than 4.7	40	10	24.1	1.0
4.7–5.1	39	10	23.8	1.1 (0.5,2.7)
5.2–6.1	233	89	35.6	1.6 (0.9,3.2)
6.2 or greater	413	122	26.3	1.2 (0.6,2.3)
Lower activity				
Less than 4.7	15	7	78.2	1.0
4.7–5.1	17	5	31.6	0.2 (0.1,0.8)
5.2–6.1	33	10	34.9	0.3 (0.1,0.8)
6.2 or greater	65	30	48.6	0.3 (0.1,0.8)

** Models adjusted for body mass index, diabetes, systolic blood pressure, cigarette smoking, age, and activity level.*
*** Models adjusted for body mass index, diabetes, systolic blood pressure, cigarette smoking, and age.*

TABLE 4. CORONARY HEART DISEASE INCIDENCE IN RELATION TO ACTIVITY STRATA AND SERUM CHOLESTEROL LEVEL AMONG MEN

Activity Strata and Serum Cholesterol Level (mmol/L)	*n*	Cases	Incidence per 1,000 Person Years	Relative Risk and 95% Confidence Interval
All activity levels*				
Less than 4.7	144	52	39.2	1.0
4.7–5.1	166	56	33.4	0.9 (0.6,1.3)
5.2–6.1	416	152	36.6	1.0 (0.7,1.3)
6.2 or greater	369	154	43.0	1.2 (0.9,1.7)
Stratified by activity**				
Higher activity				
Less than 4.7	55	18	31.1	1.0
4.7–5.1	66	25	35.7	1.2 (0.7,2.2)
5.2–6.1	181	63	33.5	1.1 (0.7,2.0)
6.2 or greater	149	62	40.6	1.5 (0.9,2.6)
Moderate activity				
Less than 4.7	64	21	37.3	1.0
4.7–5.1	82	24	28.6	0.8 (0.5,1.5)
5.2–6.1	203	76	37.5	1.1 (0.7,1.8)
6.2 or greater	183	78	43.7	1.4 (0.9,2.3)
Lower activity				
Less than 4.7	25	13	70.7	1.0
4.7–5.1	18	7	50.0	0.4 (0.1,0.9)
5.2–6.1	32	13	52.8	0.4 (0.2,1.0)
6.2 or greater	37	14	51.6	0.5 (0.2,1.0)

** Models adjusted for body mass index, diabetes, systolic blood pressure, cigarette smoking, age, and activity level.*
*** Models adjusted for body mass index, diabetes, systolic blood pressure, cigarette smoking, and age.*

level was similar for both men and women, the analyses were recalculated combining men and women of similar activity groups together and controlling for sex. Interaction terms for sex and serum cholesterol level within activity groups were not significant ($P = 0.58$ within the high activity group, $P = 0.17$ for moderate, and $P = 0.98$ for the low activity group).

Relative risk estimates for the high activity group of men and women showed a graded relative risk from 1.3 for those with serum cholesterol level of 4.7–5.1 to

TABLE 5. RELATIONSHIP OF CHOLESTEROL AND HEART DISEASE INCIDENCE BY ACTIVITY LEVEL FOR MEN AND WOMEN COMBINED

Cholesterol Level (mmol/L)	Activity Level*			
	All	High	Moderate	Low
Less than 4.7	1.0	1.0	1.0	1.0
4.7–5.1	0.9 (0.6,1.2)	1.3 (0.7,2.3)	0.9 (0.5,1.4)	0.3 (0.1,0.6)
5.2–6.1	1.1 (0.8,1.4)	1.5 (0.9,2.4)	1.3 (0.9,1.9)	0.3 (0.2,0.7)
6.2 or greater	1.1 (0.8,1.4)	1.7 (1.0,2.7)	1.2 (0.8,1.7)	0.4 (0.2,0.7)

* *Models adjusted for body mass index, diabetes, systolic blood pressure, cigarette smoking, age, and sex.*

1.7 for those with a serum cholesterol level of 6.2 mmol/L or more ($P = 0.04$). For those with moderate activity, risks were relatively flat; while for those of low activity, risks were inverse and all statistically significant (Table 5).

DISCUSSION

These data suggest there may be differences in the serum cholesterol-coronary heart disease association within the older population on the basis of activity level. For those of high activity, the association between serum cholesterol level and coronary heart disease risk paralleled and was of similar magnitude to other recently published studies of serum cholesterol level and coronary heart disease in older populations.[10–12] The results for the more active older people contrast with the inverse serum cholesterol-coronary heart disease relationship among older men and women of lower activity. However, as coronary heart disease rates were similar among those with high serum cholesterol level regardless of activity level, the implication of this difference in the direction of serum cholesterol level risk between activity strata is that those with low serum cholesterol level comprise two sub-populations, one with high risk of coronary heart disease and one with low risk.

Methodologic limitations in our data bear consideration. Sample size was small, especially for those with low serum cholesterol level in the stratified models. This limitation reduced the power of our analyses. One solution was to combine men and women of similar activity level which allowed a more stable estimate of risk within activity strata. Sample size considerations also limited our ability to consider estimates for populations other than whites. This limitation underscores the need for better data on cardiovascular risk factors in older persons, particularly if modifying factors, such as activity level, are a consideration.

Could incomplete case ascertainment of coronary heart disease contribute to these results? Although upwards of 20 percent of myocardial infarctions in older populations may be silent, recent data suggests that the course of these events is no different than in known myocardial infarctions.[31] Over time, then, most cases of coronary heart disease in the community should become apparent either through hospital discharge data or death certificate. Since there is no evidence that serum cholesterol level is more strongly related to silent coronary heart disease, it is unlikely that incomplete case ascertainment could account for these results. Likewise, the results appear robust in that the direction was not changed by exclusion of cases based on death certificate only or consideration of self-reports only as cases.

Activity level was selected as a potential modifier for several reasons. We were interested in whether functional health status would modify the serum cholesterol level relationship, and activity level was one of the few variables associated with physical functioning available for all persons in our data set. We had also observed that activity level appeared to vary with other health status variables within our data. For instance, fewer than 20 percent of high activity men or women had two or more medical conditions, compared with over 30 percent of low activity men or women. In a subsample of the population who received detailed examinations, those with low activity comprised a higher percent of those with fair or poor self-reported health and those who had been hospitalized in the past year. In general, activity measures have been used as indicators of physical exercise, with those who are in the low activity group regarded as choosing a more sedentary lifestyle. While it is possible that this interpretation may contribute to our findings, it is also possible that the effect of activity as a modifier may reflect health status. This latter view is supported by the consistency of our results for the active men with the results from studies of healthier older men such as the Rancho Bernardo population and the Kaiser study.[10,12]

Factors associated with low activity may depress serum cholesterol level and increase risk of coronary heart disease.[32,33] Alternatively, it is possible that the low serum cholesterol level itself may be implicated in risk of coronary heart disease as has been suggested for hemorrhagic stroke.[21] Lower HDL-cholesterol levels might also increase risk as was suggested by a recent study in which low HDL-cholesterol conferred risk even if serum cholesterol level was low.[34] Our data set, which was based on one serum cholesterol level meas-

urement in 1971–1975, does not allow us to examine change in serum cholesterol level over time, and no lipoprotein fraction data were available.

In this paper, we demonstrated that absence of an association between coronary heart disease and serum cholesterol level in older persons could be partially accounted for by modification of risk in the low serum cholesterol level group by activity level. Modification of risk relationships has been noted as a complicating factor in assessment of low body weight,[35,36] and low blood pressure[37] and our data suggest this may also be true for assessment of serum cholesterol level risk as well. The National Cholesterol Education Program guidelines acknowledge the complexity of the serum cholesterol-coronary heart disease relationship in older persons and support individualization of treatment in this group.[38] The older population has a sizeable proportion of individuals who are ill, and consideration of underlying health status may be necessary in evaluation of epidemiologic evidence of the serum cholesterol-coronary heart disease association, as well as in formulation of appropriate recommendations for screening and intervention in this population.

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APPENDIX A. EFFECT OF CHANGE IN CASE DEFINITION ON RELATIONSHIP OF SERUM CHOLESTEROL TO CORONARY DISEASE INCIDENCE WITHIN ACTIVITY STRATA

Activity Strata and Serum Cholesterol Level (mmol/L)	Example 1 Expanded Case Definition Including Self-Reports		Example 2 Excluding Death Certificate Only Cases	
	Women	Men	Women	Men
Stratified by activity*				
Higher activity				
Less than 4.7	1.0	1.0	1.0	1.0
4.7–5.1	1.9 (0.4,9.9)	1.2 (0.7,2.3)	1.4 (0.3,7.9)	1.2 (0.6,2.4)
5.2–6.1	3.9 (0.9,16.4)	1.3 (0.8,2.2)	3.2 (0.7,13.4)	1.1 (0.6,2.1)
6.2 or greater	3.5 (0.9,14.3)	1.6 (0.9,2.8)	2.5 (0.6,10.5)	1.4 (0.8,2.6)
Moderate activity				
Less than 4.7	1.0	1.0	1.0	1.0
4.7–5.1	1.3 (0.6,2.8)	0.8 (0.4,1.4)	1.5 (0.5,4.2)	0.9 (0.4,1.8)
5.2–6.1	1.5 (0.8,2.7)	1.2 (0.7,1.9)	2.2 (1.0,5.1)	1.3 (0.7,2.5)
6.2 or greater	1.1 (0.6,2.0)	1.5 (1.0,2.5)	1.7 (0.8,3.9)	1.7 (0.9,3.3)
Lower activity				
Less than 4.7	1.0	1.0	1.0	1.0
4.7–5.1	0.2 (0.1,0.7)	0.4 (0.2,1.1)	0.4 (0.1,1.8)	0.4 (0.1,1.4)
5.2–6.1	0.3 (0.1,0.9)	0.6 (0.3,1.3)	0.5 (0.1,1.9)	0.5 (0.2,1.5)
6.2 or greater	0.4 (0.2,0.9)	0.5 (0.2,1.0)	0.5 (0.1,1.5)	0.3 (0.1,1.1)

** Models adjusted for body mass index, diabetes, systolic blood pressure, cigarette smoking, and age.*