Blood Transfusion, Alcohol Use, and Anthropometric Risk Factors for Rheumatoid Arthritis in Older Women

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ABSTRACT. ***Objective.*** To evaluate whether blood transfusion, alcohol use, or anthropometric characteristics are risk factors for rheumatoid arthritis (RA) in older women.

Methods. These factors were evaluated in a prospective cohort study that was initiated in 1986, and included 31,336 women aged 55-69 years without a history of RA. Risk factor data were self-reported using a mailed questionnaire. Through 1997, 158 cases of RA meeting at least 4 of 7 American College of Rheumatology criteria were identified and validated by medical record review. The relative risk (RR) and 95% confidence interval (CI) were used as the measure of association, and were adjusted for the potential confounding effects of age, marital status, smoking history, age at menopause, and use of estrogen replacement therapy.

Results. History of blood transfusion was inversely associated with RA (multivariate RR = 0.72; 95% CI 0.48–1.08), and this association was stronger for rheumatoid factor (RF) positive disease (RR = 0.59; 95% CI 0.35–1.00). There were no associations for use of medications for hyper- or hypothyroidism or adult onset diabetes. Anthropometric factors (height, weight, body mass index, body fat distribution), leisure time physical activity, and alcohol use were not associated with risk of RA.

Conclusion. A history of blood transfusion was inversely associated with RA, particularly RF positive RA. Anthropometric factors, physical activity, and alcohol use did not influence the risk of RA in this cohort of older women. (J Rheumatol 2002;29:246–54)

Key Indexing Terms:

ALCOHOL	COHORT STUDY	OBESITY
RHEUMATOID ARTHRITIS	RISK FACTORS	TRANSFUSION

Although rheumatoid arthritis (RA) is often considered a disease of middle aged women, RA incidence increases in women until at least age 70[1]. Both genetic and non-genetic factors are thought to be important in the etiology of RA, although genetic epidemiology studies suggest that non-genetic factors may play a relatively larger etiologic role in older onset compared to younger onset RA[2,3]. While non-genetic risk factors have been evaluated as etiologic agents, including demographic factors, cigarette smoking, reproductive characteristics, and exogenous estrogen use (oral contraceptive and hormone replacement therapy), there are relatively few studies that have evaluated other potential lifestyle or medical history risk factors. In addition, as discussed by Symmons and Harrison[4], many prior studies of RA risk factors have had methodologic problems that limit interpretation. Finally, while a few etiologic studies have had a certain proportion of patients with RA onset after age 60 years[5-8], no previous studies have specifically evaluated risk factors for older onset RA.

We evaluate selected medical history factors including blood transfusions, history of thyroid disease, and adult onset diabetes, as well as alcohol use, anthropometric factors, and physical activity in the etiology of RA using a large, prospective cohort of older women. Most of these factors were postulated to influence RA development either by direct effects on the immune system or by effects on sex hormones, particularly estrogen, which indirectly modulate the immune system[4,9-11]. Our *a priori* hypotheses were that prior blood transfusion would be inversely associated with RA, while obesity and high waist-to-hip ratio would be positively associated with risk. We also evaluated previously suggested risk factors (alcohol use, thyroid disease, and adult-onset diabetes), as well as physical activity, since the latter factor influences body weight and possibly immune function.

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MATERIALS AND METHODS

Population. The Iowa Women's Health Study is a prospective cohort study initiated in 1986. A 16 page survey was mailed to 98,030 randomly selected women between the ages of 55 and 69 years who had a valid Iowa driver's license[12], which represented about 94% of all Iowa women in this age range[13]. The survey was completed by 41,836 women, giving a 42.7% response rate (Figure 1). Self-reported items on the baseline (1986) questionnaire included demographic data, medical and reproductive history, use of hormone replacement therapy, and smoking history. Transfusion history was assessed with the following questions: "have you ever received blood or had a blood transfusion?" and "how old were you when you received your first blood transfusion?" In a similar manner, participants were asked if they had been diagnosed with sugar diabetes and at what age. Those reporting age at onset of 30 years or older were classified as having adult onset diabetes.

Usual alcohol consumption was assessed as part of a semiquantitative food frequency questionnaire developed by Willett and colleagues[14]. Participants were asked to report how often, on average, over the last year they had consumed each of the following: beer (1 glass, bottle or can), red wine (4 oz glass), white wine (4 oz glass), and liquor (1 drink or shot). There were 9 possible responses, ranging from "never or less than once per month" to "six or more times per day." Daily intake of alcohol in grams was calculated by multiplying the frequency with which each specific beverage was consumed by the ethanol content of the specific beverage. This methodology was been shown to be reproducible (Pearson correlations > 0.98 across 3 repeat food frequency questionnaires) in this cohort[15]. The correlation with five 24 hour diet recall diaries was low (Pearson correlation 0.32), probably due to the limited ability of 24 hour recall methodology to capture sporadic alcohol use.

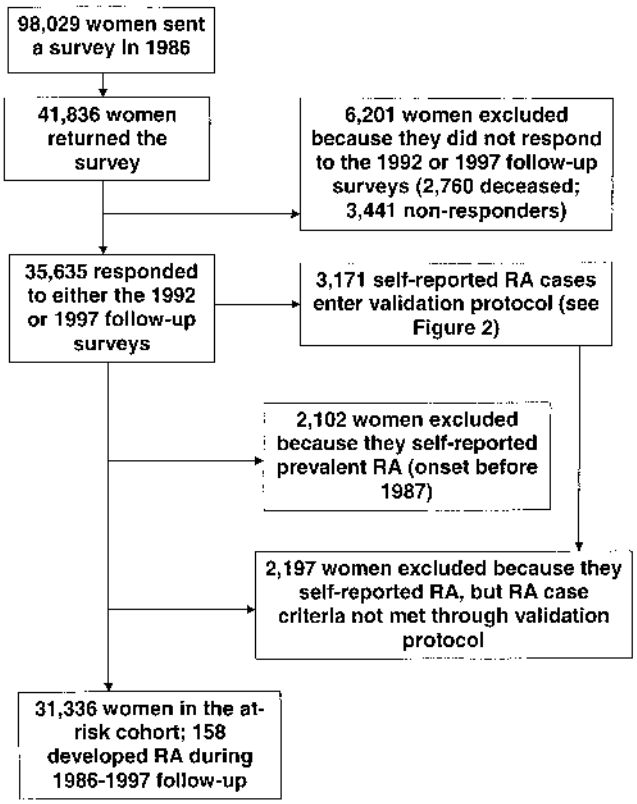

Figure 1. Sample selection for Iowa Women's Health Study, Rheumatoid Arthritis Substudy, 1986-1997.

Participants also reported current height, weight, and weight at ages 18, 30, 40, and 50 years. Body mass index (BMI) at baseline and at each respective age was calculated as weight in kilograms at a given age divided by baseline height^2 in meters. A paper tape measure and written instructions for having a friend measure circumferences of the waist (1 inch above the umbilicus) and hips (maximal protrusion) were enclosed with the questionnaire. Waist-to-hip ratio was calculated from these measures. This protocol has been shown to be valid (intraclass correlation coefficient with measures by trained technician, ≥ 0.84) and reliable (intraclass correlation of measures at 2 different time periods ≥ 0.85)[16].

Physical activity was assessed by asking participants 3 questions about whether they participated in any leisure exercise, and if so, the frequency of moderate and vigorous activities. Responses to these questions were combined to create a 3 level activity score (low, medium, high). This scale has been shown to strongly predict total mortality and cardiovascular disease mortality in this cohort[17].

Cohort followup and case identification. Mortality among members of the cohort has been continuously ascertained by annual linkages (1986–1998) to Iowa death certificate data, supplemented by linkage to the National Death Index. Followup questionnaires (response rates for living eligibles) were mailed in 1987 (91%), 1989 (89%), 1992 (83%), and 1997 (79%) to update residence and collect additional exposure and outcome data. On the 1992 questionnaire, respondents were asked "Have you ever been told by a doctor that you have rheumatoid arthritis" and "If yes, age at first diagnosis?" Of the women responding to this question, 1018 women reported a new diagnosis of RA after 1986, 1249 reported that they were "not sure" of an RA diagnosis, and 220 reported an RA diagnosis but did not give an age at diagnosis. On the 1997 questionnaire, respondents were asked "Since July 1992, were you diagnosed for the first time by a doctor as having rheumatoid arthritis?" This questionnaire identified an additional 684 potential incident cases of RA.

All women (N = 3171) with potential incident RA (onset after 1986) were contacted by mail to confirm their "yes," "not sure," or "yes" but missing age responses, to obtain the names and addresses of all physicians whom they had seen about their RA, and to obtain consent for release of their medical records. Reminder postcards were sent after the initial letter, followed by a second mailing. Non-respondents to this supplemental questionnaire were contacted by telephone. For deceased subjects, next-of-kin were contacted.

As shown in Figure 2, of the 3171 women eligible for this component of the study, only 53 (1.7%) participants or next-of-kin could not be located. An additional 162 (5.1%) refused participation, and 70 (2.2%) responded but did not provide consent for release of medical records. This yielded an overall contact rate of 98.3% and an overall participation rate of 91.0% (2886/3171). Of the women contacted, 52.3% (1659/3171) were found not to be eligible incident cases of RA, either because RA was first diagnosed before 1987 or because of the conversion of an original "not sure" response to a "no" response when recontacted.

Case validation. Medical records were requested from identified physicians to validate the diagnosis of RA for each consenting subject who confirmed their original self-report. Physicians were asked to complete a brief questionnaire and provide all medical, laboratory, and radiographic records pertinent to the diagnosis. Medical records were obtained for 1186 of the 1227 (96.7%) potential incident RA cases.

A combination of 2 trained reviewers including rheumatologists, a rheumatology advanced practice nurse, and a rheumatology physician assistant independently reviewed all medical records to determine RA case status using the "ever" (since cohort baseline) satisfaction of 4 out of 7 American College of Rheumatology (ACR) criteria[18]. Discordance between the 2 primary reviewers was adjudicated by consensus or a third reviewer. Although medical records were requested on all potential cases, any diagnosis of "definite RA" provided by a physician identified as a board-certified/eligible rheumatologist was also considered a validated case. We defined the date of RA onset as the first date of an RA symptom

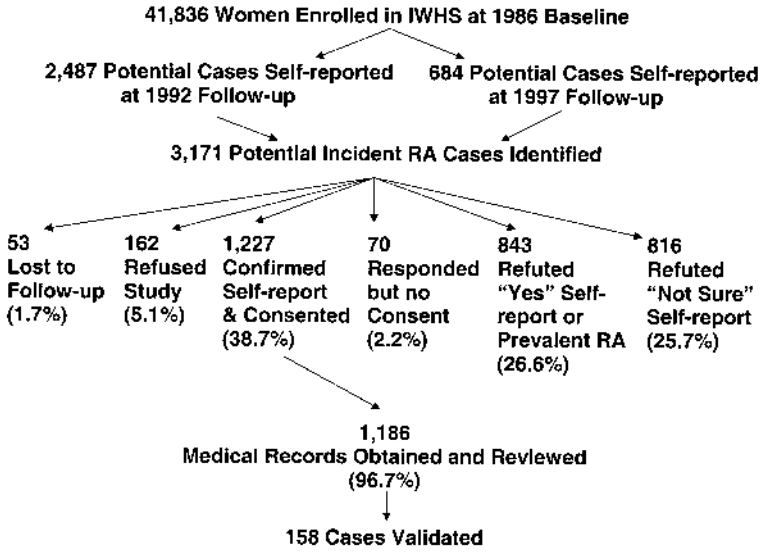

Figure 2. Validation process for potential incident cases of rheumatoid arthritis in the Iowa Women's Health Study, 1986-1997.

leading to the eventual satisfaction of ACR criteria or a rheumatologist's diagnosis of RA. Women with self-limited polyarticular arthritis (i.e., viral arthritis) or alternative diagnoses such as gout were excluded as cases. Review of these 1186 sets of records resulted in 158 validated RA cases. RA diagnosis was based on either cumulative satisfaction of the ACR criteria (n = 146) and/or diagnosis by a rheumatologist (n = 139).

Data analysis. From the original cohort of 41,836, we excluded women who did not complete either the 1992 or 1997 followup questionnaires due to death or non-response (n = 6201) or who reported that they had been diagnosed with RA and gave a diagnosis date in or before 1986 (n = 2102; no attempt at validation) (Figure 1). This left 30,362 women who reported no history of RA on the 1992 and/or the 1997 questionnaire and 3171 women in the validation component of the study. Women who had marked "not sure" of an RA diagnosis on the 1992 questionnaire, but reported "no" to RA questions on further investigation (n = 816), were added back to the at risk cohort. Thus, the final analysis cohort (n = 31,336) included women with no history of RA (n = 30,362), women added back (n = 816), and women who had validated RA (n = 158).

Each woman accumulated person-years of followup from the date of receipt of the 1986 baseline questionnaire to one of the following (in order of priority): (1) the date of RA symptom onset; (2) September 30, 1992 (date of Followup 3 questionnaire), for women who did not complete the Followup 4 questionnaire (due to death or nonresponse); or (3) August 31, 1997 (date of Followup 4 questionnaire) for all remaining women.

Exposure variables were categorized into previously published categories for physical activity and medical history variables. The anthropometric measures were categorized into quartiles based on the distribution in the at risk cohort. Daily total alcohol intake was categorized into 4 levels: no regular use and tertiles of alcohol intake among users. Individual alcoholic beverages were classified as < 1/month or never use, use < 1/week (approximate median of use among drinkers in the cohort), and use 1/week or more.

Age- and multivariable-adjusted relative risks (RR), along with 95% confidence intervals (CI), were calculated as the measure of association between the exposures of interest and RA incidence, and were estimated using Cox proportional hazards regression[19]. Multivariable models included marital status (current, widowed, separated/divorced, never), smoking history (never, former < 20 pack-years, former ≥ 20 pack-years, current < 20 pack-years, current ≥ 20 pack-years), age at menopause (continuous), and use of estrogen replacement therapy (never, former, current), factors that have been associated with RA in this cohort[20,21]. For selected exposures previously more strongly associated with rheumatoid factor (RF) positive case status (i.e., alcohol use[6] and transfusion history[7]), we conducted analyses restricting cases to RF positive status (RF negative and RF unknown cases were excluded).

RESULTS

The mean age of the 31,336 women in the at risk cohort was 61.5 years, and over 99% were white. During 334,463 person-years of followup (1986–1997), 158 validated cases of RA were identified. The mean age at symptom onset was 67.8 years (range 57–79 years), and the onset of symptoms was 1.1 ± 1.8 years before definitive diagnosis (median 5 mo, range 0–12.2 yrs). This diagnostic lag period is highly consistent with data from other population-based studies[22,23]. Of the 158 cases, 61% were RF positive, 31% were RF negative, and 8% had unknown RF status.

Medical history risk factors are presented in Table 1. There was no association for use of thyroid medications (for hypo or hyperthyroidism), or history of adult onset diabetes. There was a suggestive inverse association with ever having received a blood transfusion (RR = 0.77; 95% CI 0.53–1.13), and the association was stronger for RF positive cases (RR = 0.63; 95% CI 0.37–1.04). When evaluating year of first transfusion, women receiving their first transfusion from 1982–1986 (< 5 years before study baseline) were at slightly elevated risk of RA (RR = 1.31; 95% CI 0.48–3.55), while those receiving their first transfusion from 1957–1981 (5–29 years before study baseline) were at lower risk of RA (RR = 0.69; 95% CI 0.41–1.14) as were those receiving their first transfusion before 1957 (≥ 30 years before study baseline) (RR = 0.83; 95% CI 0.47–1.49). When the analysis was restricted to RF positive cases, the RR were 1.00 (95% CI

Table 1. Age-adjusted relative risks (RR) of rheumatoid arthritis in relation to selected medical history factors, Iowa Women's Health Study, 1986–1997.

Medical History Factor at Baseline	Cases	Person-Years	RR	95% CI
Adult onset diabetes				
No	152	316401	1.00	Reference
Yes	6	14548	0.88	0.39–2.00
Use of thyroid medications				
Hypothyroidism				
No	126	274971	1.00	Reference
Yes	26	47266	1.21	0.79–1.84
Hyperthyroidism				
No	145	304824	1.00	Reference
Yes	6	14713	0.87	0.38–1.96
Blood transfusion				
Never	119	235266	1.00	Reference
Ever	34	87062	0.77	0.53–1.13
Year of first transfusion (time from first transfusion to baseline survey)				
1982–1986 (< 5 yrs)	4	6108	1.31	0.48–3.55
1957–1981 (5–29 yrs)	17	48706	0.69	0.41–1.14
< 1957 (≥ 30 yrs)	13	30895	0.83	0.47–1.49

95%CI: 95% confidence interval.

0.25–4.08), 0.43 (95% CI 0.20–0.94) and 0.89 (95% 0.44–1.77) for 1982–1986, 1957–1981, and < 1957, respectively.

With respect to anthropometric factors (Table 2), there were no associations for height, weight, BMI, or past BMI (i.e., at ages 18, 30, or 50 years). There was no association with waist-to-hip ratio (Table 2) or with waist or hip circumference per se (data not shown). There was also no association with level of physical activity.

With respect to alcohol use (Table 3), there was no association with daily alcohol intake. There was also no association with specific types of alcoholic beverages including beer, red wine, white wine, or liquor. These findings were essentially unchanged when we restricted the analyses to RF positive cases (data not shown).

We next adjusted history of blood transfusion for age, marital status, smoking history, age at menopause, and use of estrogen replacement therapy (Table 4), factors previously associated with risk of RA in this cohort. Women who ever received a blood transfusion remained at lower risk of RA (RR = 0.72; 95% CI 0.48–1.08). When restricting the analysis to RF positive cases, the inverse association for blood transfusion was more pronounced (RR = 0.59; 95% CI 0.35–1.00), particularly for women who received their first transfusion 5–29 years before baseline (RR = 0.41; 95% 0.19–0.91). Further adjustment for either history of hysterectomy or number of pregnancies (2 conditions potentially associated with the need for a blood transfusion) did not alter these results (data not shown).

DISCUSSION

We found a suggestive inverse association for prior blood transfusion, which became stronger and statistically significant when we restricted the analyses to RF positive cases. Multivariate adjustment for other RA risk factors in this study slightly strengthened the associations. In contrast, we found no association for anthropometric factors (including height, body mass, and body fat distribution), leisure time physical activity, alcohol use, or other selected medical history factors (thyroid disease, adult onset diabetes). Strengths of this study include the prospective cohort design, rigorous case validation using ACR criteria, community setting, and validated assessment of several exposure variables (i.e., body circumferences and alcohol use). We also had sufficient statistical power (80%) to detect meaningful RR for the anthropometric variables ($RR_{\text{high vs lowquartile}}$ = 1.8), alcohol use ($RR_{\text{none vs > 7 g/day}}$ = 1.7), physical activity ($RR_{\text{none vs high}}$ = 1.7), blood transfusion ($RR_{\text{never vs ever}}$ = 1.6), and adult onset diabetes or hyperthyroidism ($RR_{\text{ever vs never}}$ = 2.3).

There are several limitations to this study that require comment. The baseline survey had a 43% response rate, and this may limit generalizability. However, respondents and nonrespondents to the baseline survey showed only minor demographic differences[12] and, with the exception of smoking-related cancers, have had similar cancer morbidity and overall mortality rates[24]. That the cohort consisted of mainly white, older Midwest women also limits generalizability, although older women have some of the highest rates

Table 2. Age-adjusted relative risks (RR) of rheumatoid arthritis in relation to selected anthropometric characteristics and physical activity, Iowa Women's Health Study, 1986–1997.

Factor	Cases	Person–Years	RR	95% CI	*p*-value for Trend
Weight (pounds) at baseline					
< 131	47	82606	1.00	Reference	
131–146	31	83772	0.66	0.42–1.04	
147–166	37	84573	0.78	0.51–1.21	
> 166	43	83512	0.92	0.61–1.39	0.88
Height (inches) at baseline					
< 62	25	39960	1.00	Reference	
62–63	42	95823	0.70	0.42–1.16	
64–65	50	100951	0.87	0.69–1.11	
> 65	41	97730	0.90	0.79–1.02	0.21
BMI (kg/m^2) at baseline					
< 23.4	41	82246	1.00	Reference	
23.4–25.8	36	84646	0.88	0.56–1.37	
25.9–29.2	40	83761	0.99	0.64–1.53	
> 29.2	41	83810	1.01	0.65–1.56	0.76
Waist to hip ratio at baseline					
< 0.773	45	84038	1.00	Reference	
0.773–0.825	44	84158	1.01	0.67–1.54	
0.826–0.886	33	82845	0.78	0.49–1.22	
> 0.886	36	82365	0.86	0.55–1.34	0.28
BMI (kg/m^2) at age 18					
< 19.6	39	83037	1.00	Reference	
19.6–21.1	47	83976	1.16	0.76–1.78	
21.2–22.9	34	83002	0.87	0.55–1.37	
> 22.9	38	83060	0.97	0.62–1.51	0.97
BMI (kg/m^2) at age 30					
< 21.2	39	83037	1.00	Reference	
21.2–22.6	42	80945	1.09	0.71–1.69	
22.7–24.6	35	85586	0.84	0.53–1.33	
> 24.6	42	80786	1.10	0.71–1.69	0.92
BMI (kg/m^2) at age 50					
< 22.7	38	80760	1.00	Reference	
22.7–24.8	38	87397	0.90	0.57–1.42	
24.9–27.5	45	83526	1.15	0.75–1.77	
> 27.5	37	81938	0.96	0.61–1.50	0.87
Physical activity index					
Low	76	149932	1.00	Reference	
Moderate	40	92539	0.84	0.57–1.23	
High	39	86012	0.90	0.61–1.32	0.51

95% CI: confidence interval, BMI: body mass index.

of RA. There was also an opportunity for non-response during the various phases of followup to identify and validate the RA cases in the cohort, which could introduce bias. However, we had high response rates to each phase of the study, and it seems unlikely that this would introduce a large, systematic bias into our results. Another potential weakness relates to the fact that we did not clinically examine each case. However, given the rigorous case validation methods, it seems highly unlikely that we have incorrectly classified subjects as RA cases. Conversely, it is possible that individuals with milder RA or those not seeking medical attention have been misclassified; however, the large group of non-cases used for the comparison group makes false negatives a minor concern in this analysis. Finally, misclassification of the main (self-reported) exposures of interest leading to an inability to detect an association with RA is a potential limitation. However, many of the exposures evaluated here have shown associations with other outcomes in a manner consistent with previous literature (e.g., BMI, physical activity, adult onset diabetes and alcohol use with coronary heart disease mortality[17]), suggesting that the latter bias is unlikely to be large.

A direct comparison of our results with other studies is somewhat limited, since this study specifically focuses on RA development in older women. Nevertheless, many previous studies have had a varying proportion of RA cases

Table 3. Age-adjusted relative risks (RR) of rheumatoid arthritis in relation to level of intake of alcoholic beverages, Iowa Women's Health Study, 1986–1997.

Factor	Cases	Person-Years	RR	95% CI	p–value for Trend
Alcohol, g/day					
Non-drinkers	82	166582	1.00	Reference	
< 2	18	47643	0.77	0.46–1.27	
2–7	32	51593	1.21	0.80–1.83	
> 7	20	48364	0.83	0.51–1.36	0.85
Beer (1 glass, bottle, can)					
< 1/month or never	125	256973	1.00	Reference	
< 1/week	14	26709	1.08	0.62–1.88	
1/week or more	13	30500	0.88	0.49–1.56	0.76
Red wine (4 oz glass)					
< 1/month or never	118	242103	1.00	Reference	
< 1/week	24	50047	0.99	0.64–1.53	
1/week or more	10	22031	0.93	0.49–1.78	0.84
White wine (4 oz glass)					
< 1/month or never	117	240009	1.00	Reference	
< 1/week	20	44642	0.92	0.57–1.48	
1/week or more	15	29530	1.04	0.61–1.79	0.99
Liquor (1 drink or shot)					
< 1/month or never	112	228734	1.00	Reference	
< 1/week	14	36279	0.78	0.45–1.37	
1/week or more	26	49168	1.03	0.67–1.60	0.92

95% CI: 95% confidence interval.

that were over the age of 55 years. Some studies have suggested that elderly onset RA may have a distinct clinical presentation (abrupt onset, absence of serum RF, less common occurrence of subcutaneous nodules) and may also have a poorer outcome and faster functional decline[1,25-27], although this is controversial. In addition, while the presentation and outcome of elderly onset RA may differ from younger onset RA[2,3], there is currently no *a priori* reason to suspect that environmental risk factors *per se* operate differently, although the relative role of non-genetic factors may be somewhat greater in elderly onset RA[2,3]. A rigorous test of this hypothesis, however, is currently lacking.

Transfusion history and other medical history factors. We found an inverse association of blood transfusion with risk of RA, one of our *a priori* hypotheses. The strongest inverse association was seen for RF positive cases and for transfusion given 5–29 years before the study baseline. In contrast, Symmons, *et al*[7] found a positive association with prior blood transfusion and risk of RA in a case control study conducted in Norfolk, England (OR = 4.83; 95% CI 1.29–18.07). Most patients with RA in that study were transfused more than 10 years before symptom onset, and the association was somewhat stronger for RF positive cases and among women. The reasons for the opposite results from our study is unclear, but could be due to methodologic differences in the studies, actual differences in transfusion practice in the United States and Britain, some other factor, or chance. There were also differences in the prevalence of

Table 4. Multivariate relative risks (RR)* of rheumatoid arthritis in relation to selected medical history factors, Iowa Women's Health Study, 1986–1997.

	All Cases		RF Positive Cases	
	RR	95% CI	RR	95% CI
Blood transfusion				
Never	1.00	Reference	1.00	Reference
Ever	0.72	0.48–1.08	0.59	0.35–1.00
Time from first transfusion				
1982–1986 (< 5 yrs)	1.45	0.53–3.94	1.06	0.26–4.34
1957–1981 (5–29 yrs)	0.65	0.38–1.11	0.41	0.19–0.91
< 1957 (≥ 30 yrs)	0.71	0.38–1.30	0.78	0.38–1.59

* Adjusted for age, marital status (current, widowed, separated/divorced, never), smoking history (never, former < 20 pack-years, former ≥ 20 pack-years, current < 20 pack-years, current ≥ 20 pack-years), age at menopause (continuous), and use of estrogen replacement therapy (never, former, current). 95% CI: 95% confidence interval.

blood transfusion between the 2 studies. In the Iowa Women's Health Study, 18.9% (34/156) of the RA cases reported a history of transfusion compared to 26.3% (8162/31,003) of the non-cases. This rate in the non-cases is consistent with some national data[28]. In the Norfolk study, 18.9% of the RA cases (17/90) similarly reported a history of blood transfusion (6/93) compared to only 6.5% of the controls; sex-specific data were not available. Thus, a possible explanation for the positive association in the Norfolk study is that a history of transfusion may be unusually low in the control group, inflating their estimate of effect.

Allogeneic blood transfusion has clinically important immunomodulatory effects, which may last for years or decades[29,30]. For example, allogenic blood dramatically decreases allograft rejection[31], may decrease recurrent spontaneous abortions[32], and has been associated with longer remission in Crohn's disease[33,34]. This immunomodulatory effect appears to be somewhat stronger with whole blood transfusion, does not occur with autologous transfusion, and has been most closely associated with the leukocyte fraction[29]. Allograft survival can be significantly improved by a pre-transplantation blood transfusion if the donor and recipient share at least one HLA-DR antigen[35] and are mismatched for the other one, a situation that appears to mimic an immunologic mechanism active in pregnancy[36]. Amelioration of RA during pregnancy is associated with maternal-fetal disparity in HLA-DR and DQ antigens[37] and maternal-fetal HLA incompatibility may postpone the risk of RA onset[38].

While the exact mechanisms responsible for the immunomudulatory effects of allogeneic blood transfusion are not known, current evidence suggests that allogeneic transfusion shifts the immune response towards a Th2 type response (secretion of interleukin 4 (IL-4), IL-5, IL-6, and IL-10) and away from a Th1 type response (secretion of IL-2, interferon-γ, and tumor necrosis factor-ß)[29,30]. This Th2 pattern is associated with an overall decrease in the proinflammatory, cell-mediated immune response and the upregulation of the humoral response (i.e., antibody production), which is the pattern typical of pregnancy and opposite of that seen in RA, typically considered to be a Th1 related disease[11].

Allogeneic blood may also influence RA outcome. In a double blind pilot study of patients with active RA, patients who were randomly assigned to one blood transfusion (matched for one HLA-A, -B, or -DR antigen and mismatched for the other antigen) showed stronger improvement on the Health Assessment Questionnaire, Ritchie Index, and visual analog scale pain scores over 6 month followup compared to placebo[39].

We found no association of use of medications for either hyper or hypothyroidism or adult onset diabetes, consistent with the only other study to evaluate these factors[7].

Obesity, body fat distribution, and physical activity. We found no association of RA with BMI, which we *a priori* hypothesized would be positively associated with RA since obesity increases endogenous estrogen levels in postmenopausal women[40]. Three of 3 case control studies[6-8], but only 1 of 3 cohort studies ([5,41], plus current study) have reported positive associations of BMI with RA, with odds ratios ranging from 1.8 to > 3. The single positive cohort study[41] did not validate all their cases, but it is not clear that this would systematically bias their results. For the case control studies, all 3 used recently diagnosed cases, and had reasonably high response rates. Most[5-8] but not all[41] studies included RA cases over age 55 years, although none of them specifically reported age-stratified results. However, Voight and colleagues[6] found a stronger association for body mass at maximum lifetime weight with RA among premenopausal women relative to postmenopausal women, suggesting the possibility that body mass is more important in younger-onset RA. Two studies[7,8] found that the elevated risk of RA was specifically associated with obesity (i.e., BMI > 30 kg/m^2), although both null studies (the current study and Hernandez, *et al*[5]) had sufficient power to detect a relative risk of greater than 2 in women at this level of BMI. It seems unlikely that we were unable to detect an association due to exposure misclassification, as BMI is strongly correlated with breast and endometrial cancer incidence[12,42] and coronary heart disease mortality[17] in this cohort.

Other anthropometric variables have been less frequently evaluated. Voight, *et al*[6] reported no association between body mass at age 18 and RA, consistent with our results. Vessey, *et al*[41] reported no association with height and RA, also consistent with our findings. To our knowledge, no prior study has evaluated body fat distribution and risk of RA. We hypothesized that abdominal adiposity might be positively associated with RA since it is associated with several other chronic diseases (e.g., breast cancer, diabetes, heart disease), possibly due to the effects of higher levels of free testosterone and estradiol and lower sex hormone binding globulin relative to those with gluteal adiposity[43]. However, our study suggests that body fat distribution is not likely to be an important determinant of risk, at least for RA in women.

To our knowledge, no previous study has evaluated physical activity with risk of RA. Our data suggest that it is not an important factor, at least for leisure time activity levels in the postmenopausal years.

Alcohol use. We found no association between alcohol use in 1986 and RA, either when assessed as total alcohol consumed (g/day), or for specific alcoholic beverage subtypes. There was also no association with alcohol use when we restricted our analysis to RF positive cases. We did not, however, have lifetime consumption patterns, and, overall, use of alcohol was relatively low in our cohort. Our results are in contrast to the results of 2 case control studies.

Hazes and colleagues[44] reported that compared to no use of alcoholic beverages, persons drinking 1–2 beverages/day (OR = 0.62; 95% CI 0.40-0.98) or ≥ 3 beverages/day (OR = 0.31; 95% CI 0.13–0.74) were at lower risk of RA after adjustment for year of birth, age at onset of symptoms, marital status, parity, cigarette smoking, menopausal status, and use of oral contraceptives. However, alcohol consumption in that study was determined after the diagnosis of RA, and cases may have been more likely to discontinue alcohol use after symptom onset and initiation of pharmacologic treatments.

In a case control study conducted in Seattle, Voight and colleagues[6] found no overall association with current alcohol use and RA, with current alcohol use defined as use one year before RA symptom onset. However, they did report an inverse association for alcohol use among postmenopausal women who were RF positive (OR = 0.6; 95% CI 0.3–1.1). There was also a suggestive inverse association of lifetime average number of alcoholic drinks per week and risk of RA among postmenopausal, but not premenopausal, women, and this association was stronger for RF positive cases. No single type of alcoholic beverage was specifically associated with RA.

A mechanistic basis for a role of alcohol in the etiology of RA has not been well developed. Alcohol is thought to have effects on both the hormonal and immunologic systems, although the current knowledge is incomplete and often conflicting. For example, in postmenopausal women, alcohol has been associated with an increase, a decrease, as well as no change in serum or urinary estrogens[45]. From an immunologic perspective, heavy alcohol consumption suppresses immunity[46], but less is known about the immunomodulatory effects of light-to-moderate alcohol consumption (i.e., social drinking). Social drinking has been shown to impair lymphokine-activated killer activity, but not natural killer activity[47]; however, data are limited.

Consistent with our *a priori* hypothesis of an inverse association of blood transfusion, and supported by a biologic rationale, we found an inverse association with this risk factor. However, given the conflicting data with the only other published study, further epidemiologic data are needed to clarify this putative association. In contrast, our data do not support a role for anthropometric factors, physical activity, or alcohol consumption in the etiology of RA among older women.

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