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acute bronchitis (5 patients, 0.8 events per 100 patient-years), and pyelonephritis (3 patients, 0.5 events per 100 patient-years).

Four malignancies were reported in 4 patients (2.8%; 0.7 events per 100 patient-years). The types of malignancies were bladder cancer, breast cancer, large intestine carcinoma, and intraductal papilloma.

Temporary prolongation of treatment intervals with tocilizumab was observed throughout the study. Although 163 events of prolonged intervals of 8 weeks or more occurred, the majority of the prolongation of intervals were due to transition from the randomised study to the extension study (median interval of the transition was 10.1 weeks). No particular adverse events were reported when tocilizumab was readministered except for one patient with a severe infusion reaction. The patient had received 4 mg/kg of tocilizumab in the initial 3-month trial, and IgE anti-tocilizumab antibodies appeared at the second infusion of the extension trial. Two more patients were positive for anti-tocilizumab antibodies, when tocilizumab was not detectable in their blood. No adverse event was reported related to the anti-tocilizumab antibodies.

Mean non-fasting total blood cholesterol increased after treatment initiation and stabilized (mean values, 185 mg/dL at base line; 220 mg/dL at 12 months; 214 mg/dL at 60 months; Figure 2-A). One hundred and twelve patients experienced total cholesterol abnormalities at least one point, and 15 patients of them had abnormal values at baseline. Thirty-nine patients (34.8%) were treated with statins, including 2 patients who had started statin treatment before the trial. There was no cardiovascular SAE related to tocilizumab except for ischemic heart disease reported in one patient whose total blood cholesterol increased from 168mg/dL at baseline to 227mg/dL without statin treatment . The patient also had the risk factor of diabetes mellitus.

Mean neutrophil counts decreased but remained within the normal range (Figure 2-B). Grade 2 neutropenia was observed in 17 patients, and Grade 3 in 9 patients. All the events were transient, and no patients experienced febrile neutropenia or withdrew due to neutropenia.

Mean AST and ALT increased slightly, but remained roughly within the normal ranges (Figure 2-C). Grade 2 or higher increases in AST and ALT occurred in 9 (6.3%) and 14 (9.8%) of 143 patients, respectively, during the study, but most were transient and resolved without any particular treatment. No serious liver disorders, such as fulminate hepatitis, were seen during this study.

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Table 2. Serious adverse events (SAEs) observed in at least 1 % of patients

		%
Any SAE	77	53.8
Joint surgery	20	(14.0)
Pneumonia	9	(6.3)
Herpes zoster	7	(4.9)
Tendon rupture	5	(3.5)
Humerus fracture	4	(2.8)
Spinal osteoarthritis	3	(2.1)
Femoral neck fracture	3	(2.1)
Joint dislocation	2	(1.4)
Back pain	2	(1.4)
Lumbar spinal stenosis	2	(1.4)
Bronchitis acute	2	(1.4)
Pyelonephritis	2	(1.4)
Brain stem infarction	2	(1.4)
Cataract	2	(1.4)
Pneumothorax	2	(1.4)
Liver function abnormality	2	(1.4)

Efficacy. The response rate according to the ACR improvement criteria increased during the initial year and remained constant throughout the study period (Figure 3-A). At 5 years, 79 (84.0%), 65 (69.1%), and 41 (43.6%) of 94 patients met ACR20, ACR50, and ACR70, respectively. These response rates analysed with the last observation carried forward were 77.3%, 58.9%, and 37.6%, respectively.

Tocilizumab treatment significantly improved all measures, including tender joint counts, swollen joint counts (Figure 3-B), CRP levels (Figure 3-C), MHAQ score (Figure 3-D), and DAS28 score (Figure 3-E), and the efficacy was sustained through the 5-year treatment. The percentage of patients who achieved clinical remission defined as DAS28 <2.6 [13, 14] was 55.3% (52/94) at 5 years. Most patients exhibited anemia at baseline, and the mean hemoglobin (Hb) level was 11.3mg/dL (SD=1.4). Tocilizumab treatment significantly improved anemia in these patients, and the mean Hb level was increased to 13.2mg/dL (SD=1.5) at year 5 (Figure 3-F).

Eighty-eight of the 94 patients who received tocilizumab for more than 5 years had received corticosteroids when they began the initial study. After 5 years of tocilizumab treatment, 78/88 (88.6%) had been able to decrease their corticosteroid dose, and 28/88 (31.8%) had discontinued corticosteroids. The mean dose of corticosteroids for these patients decreased from 6.9mg/day (median 7.5mg/day) to 2.4mg/day (median 2.0mg/day) at 5 years.

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DISCUSSION

The STREAM study is the first study demonstrating the long-term safety and efficacy of tocilizumab monotherapy. This open-label extension trial of tocilizumab demonstrated a sustained good efficacy and a generally good safety profile over 5 years. The high retention rate at 5 years indeed indicates the favorable efficacy and safety profile. In particular, only one of 143 patients withdrew due to unsatisfactory response, indicating that no general loss of response occurred during long-term treatment.

ACR responses and improvement in DAS28 scores and individual components of the ACR core set were all sustained during the long-term treatment with tocilizumab monotherapy. Indeed, at 5 years, approximately half of patients had achieved ACR70, and more than half of patients had achieved clinical remission defined as the DAS28 < 2.6, although this study was open-labeled.

Tocilizumab monotherapy markedly improved inflammation markers such as CRP and ESR, and improvements were sustained throughout the study. Hemoglobin levels were also improved. It is well documented that hepcidin has a key role in anemia of chronic inflammatory diseases. IL-6 induces the secretion of hepcidin, an iron regulatory peptide hormone that is produced in the liver and that negatively regulates the absorption of intestinal iron and iron recycling by macrophages [17]. This increase in hemoglobin levels is expected to contribute to the improvement of patient QOL.

A steroid-sparing effect was another benefit of tocilizumab therapy for RA patients. Since use of corticosteroids is often associated with adverse events such as infection or steroid-induced osteoporosis, this also contributes to the improvement of patients' QOL from the safety point of view.

A major objective of this study was to evaluate long-term safety. Long-term treatment with tocilizumab was well tolerated. Most of the adverse events were mild and acceptable relative to the benefit provided. The rate of serious infections of 5.7/100 patient-years after 612 patient-years of treatment was comparable to that reported with TNF antagonists [18,19]. There was no systemic opportunistic infection or tuberculosis in this study. At least 2 patients with a history of tuberculosis were treated with tocilizumab because this study didn't exclude patients who had a history of tuberculosis. But neither had any recurrence or exacerbation of tuberculosis without prophylactic use of anti-tuberculosis drugs. However, two cases of tuberculosis were reported in another study (2 cases in 1891 patient-years in Japan)[20], and therefore we should carefully follow patients during tocilizumab treatment.

Four malignancies were reported in 4 patients. Yamanaka et al. reported a comparison of the incidence of malignancies in the following three populations; 1) tocilizumab cohort: all clinical trials (including this trial) of tocilizumab in active RA patients, 2) IORRA cohort: an observational cohort of RA patients in the Institute of Rheumatology, Tokyo Women's Medical University, and 3) a Japanese population database: cancer incidence in Japan by the research group for population-based cancer registration in Japan supported by the Japanese Ministry of

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Health, Labour and Welfare [21]. The incidence of malignancies in the patients receiving tocilizumab was almost equivalent to that in the observational cohort of RA patients or the Japanese population data. Further study will be required to evaluate whether or not tocilizumab treatment might influence the incidence of malignancies using a much larger population of RA patients treated with tocilizumab.

Throughout long-term treatment, a serious infusion reaction was observed in only one patient who received 4mg/kg of tocilizumab in the initial double-blind trial and developed IgE anti-tocilizumab antibodies. Maini et al. reported that anaphylaxis and anaphylactoid reactions occurred only at low doses of tocilizumab in the absence of MTX [6]. Therefore, initial treatment with a relatively low dose (4mg/kg) of tocilizumab without MTX may induce anti-tocilizumab antibodies.

Increases in total cholesterol, HDL cholesterol and triglycerides were observed in the initial controlled study. In this extension study, however, they did not continue increasing. Furthermore, the atherogenic index, calculated by (TC-HDLC)/HDLC, was stable through the 5-year treatment. Therefore, an increase in total cholesterol does not always mean an increased risk for cardiovascular disease. Since IL-6 is thought to play a causative role in atherosclerosis, IL-6 blockade may decrease the incidence of cardiovascular events as observed with anti-TNF therapy [22]. Further investigation will be required to evaluate whether or not tocilizumab might increase the risk for developing ischemic heart disease. Presently, we should introduce treatment according to the guideline for cholesterol management.

Neutropenia was also reported, as seen in previous studies [4-7, 9], but the incidence was less frequent than that observed in combination with MTX therapy [6, 7, 9]. This may be an advantage of tocilizumab monotherapy.

While it is established that TNF inhibitors should be given with MTX for maximal efficacy [15, 16], this study indicated that tocilizumab monotherapy offered a good safety profile and sustained efficacy throughout long-term treatment. Therefore, tocilizumab has considerable clinical benefit for patients who do not tolerate MTX. Short-term safety and efficacy studies of tocilizumab in combination with MTX or DMARD have been reported [6-9], but further studies are required to determine long-term safety and efficacy.

In conclusion, this study clearly demonstrates excellent long-term efficacy and generally good safety of tocilizumab monotherapy in active RA patients.

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Competing interests: NN has served as a consultant to and received honoraria from Chugai

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Pharmaceutical, the manufacturer of tocilizumab. NN also works as a scientific advisory board of Hoffmann-La Roche who develops tocilizumab in collaboration with Chugai Pharmaceutical Co., Ltd.. The other authors have no competing interests.

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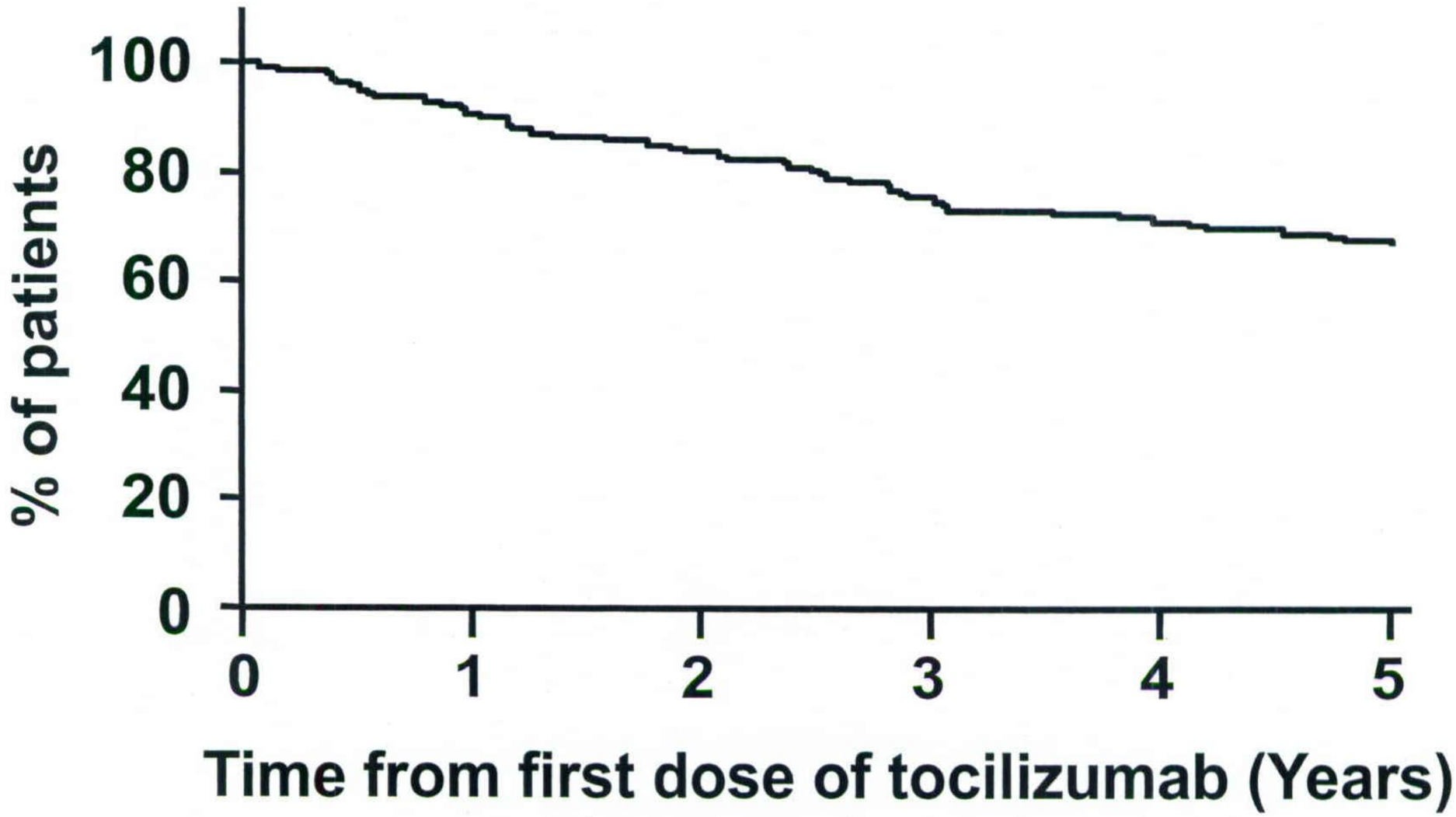
FIGURE LEGENDS

Figure 1. Kaplan-Meier estimate of the probability of the patients remaining on study.
Treatment time was calculated beginning with the first infusion of tocilizumab at any dose, excluding the time receiving placebo.

Figure 2. Change in serum total cholesterol, HDL-cholesterol, neutrophil counts, AST, and ALT.
Values are means. Bars indicate SD.

Figure 3. Percentage of responders according to the ACR improvement criteria and the Disease Activity Score in 28 joints (DAS28) as well as mean change in Modified Health Assessment Questionnaire (MHAQ) scores, number of tender joints, number of swollen joints, CRP, and hemoglobin. BL = base line

Nishimoto et al., Fig. 1



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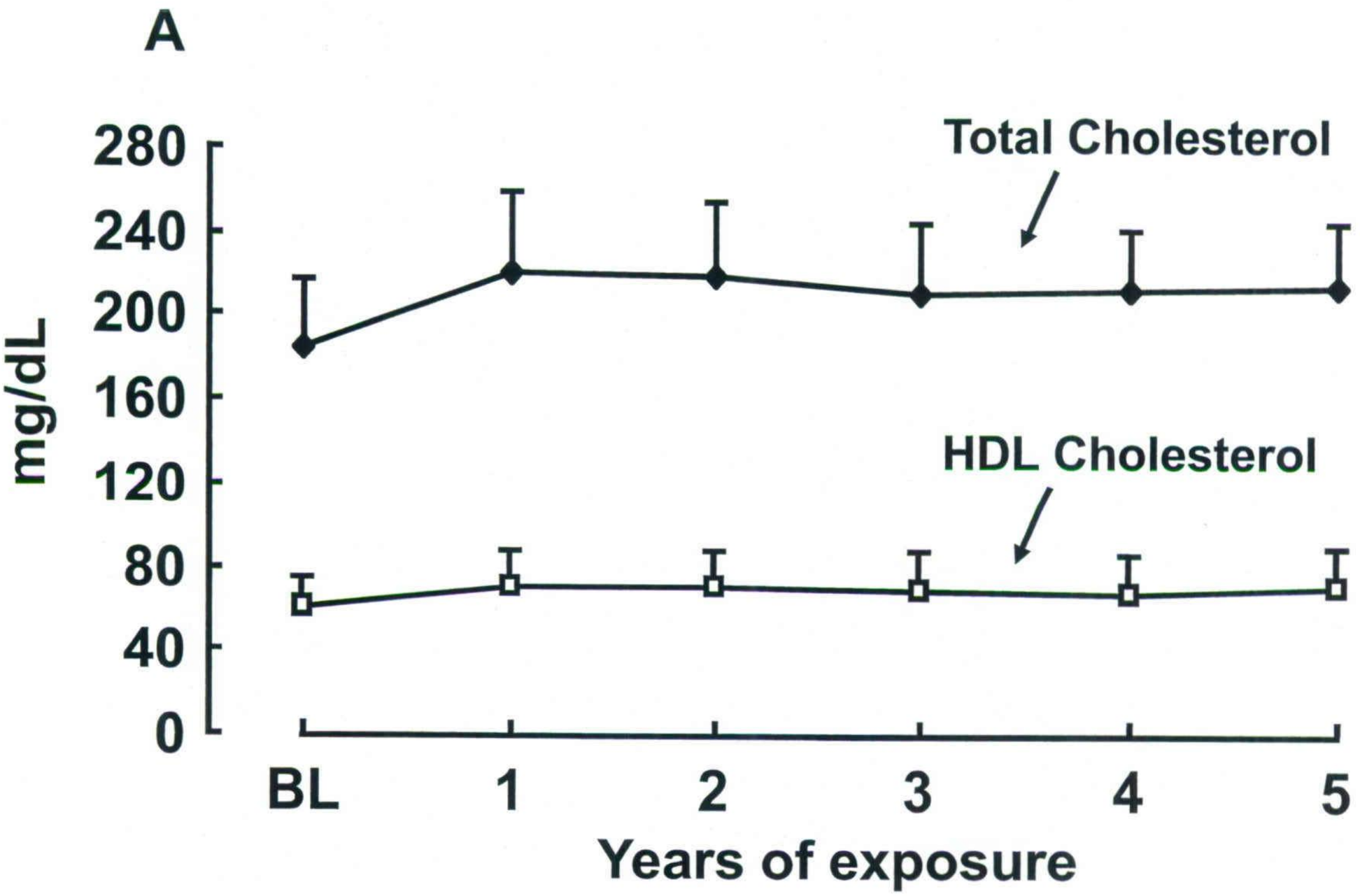

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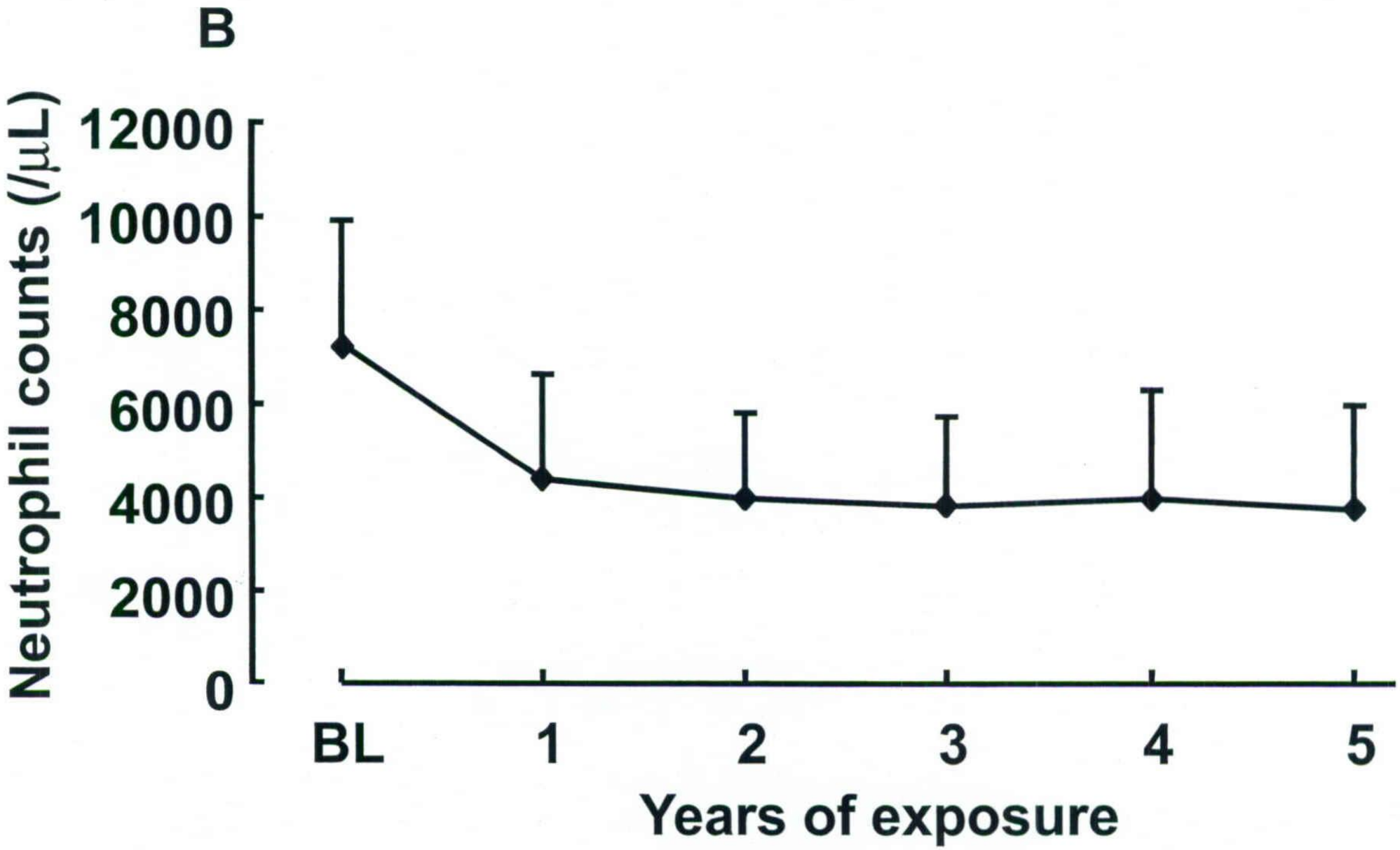

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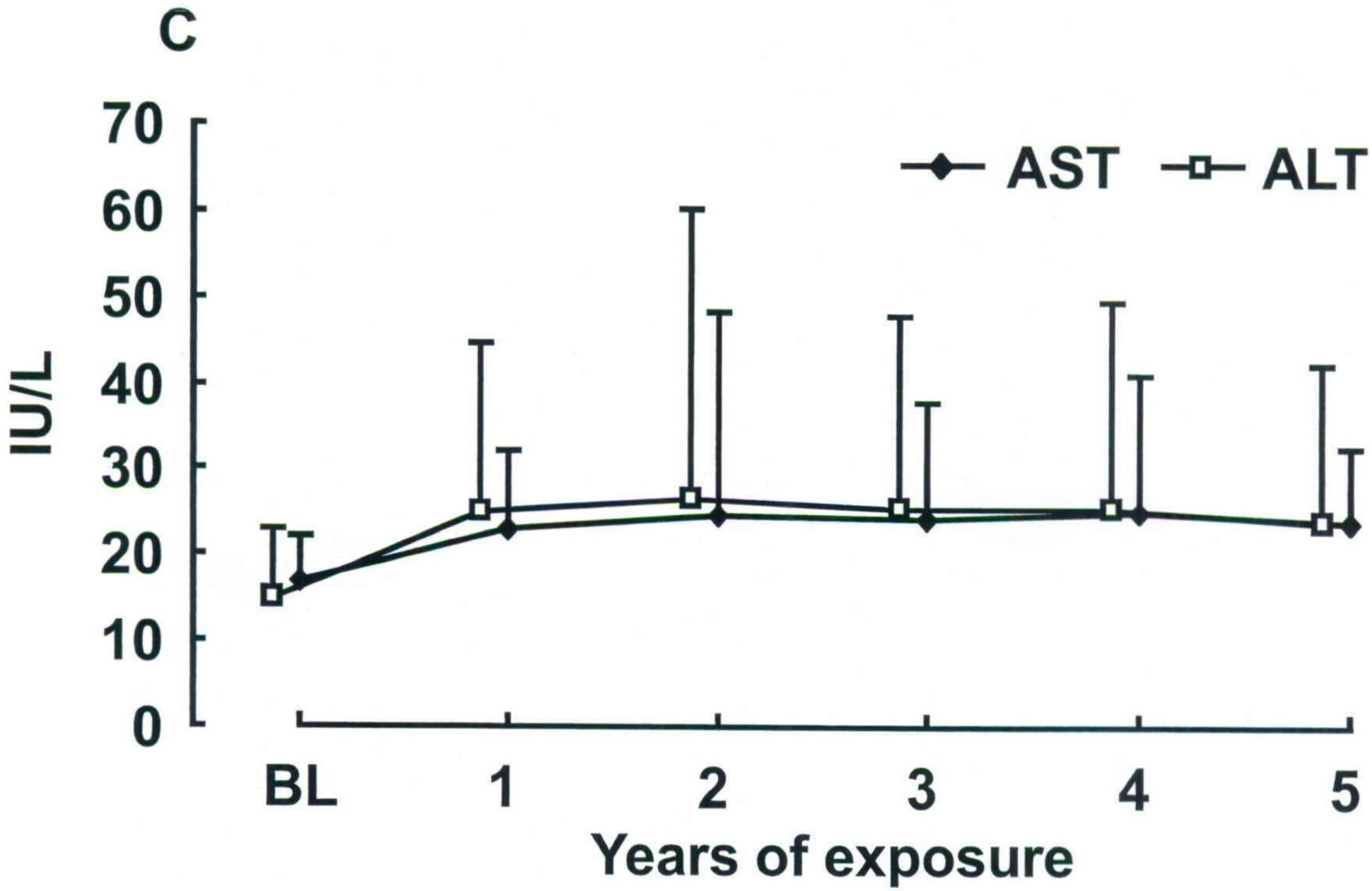

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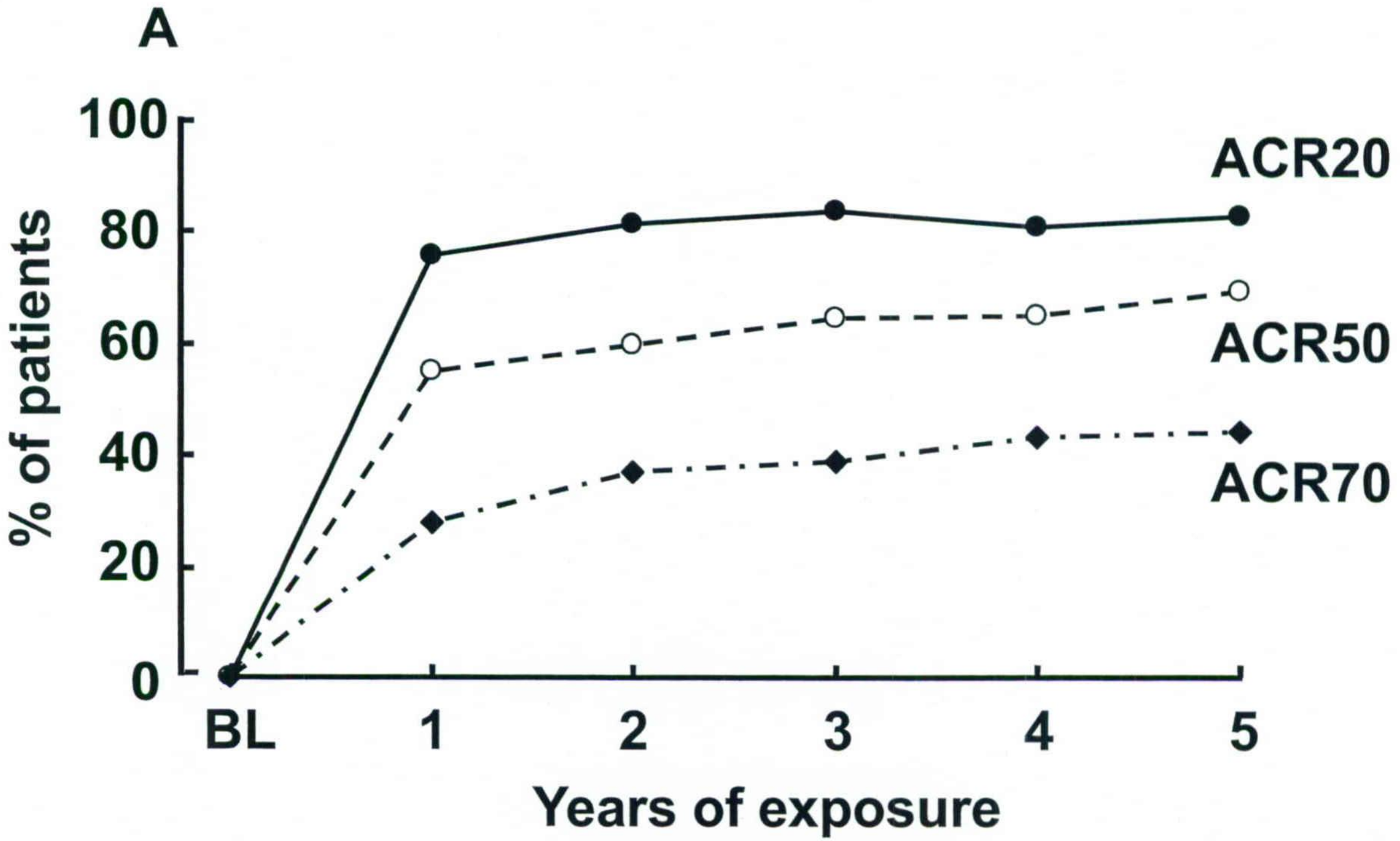

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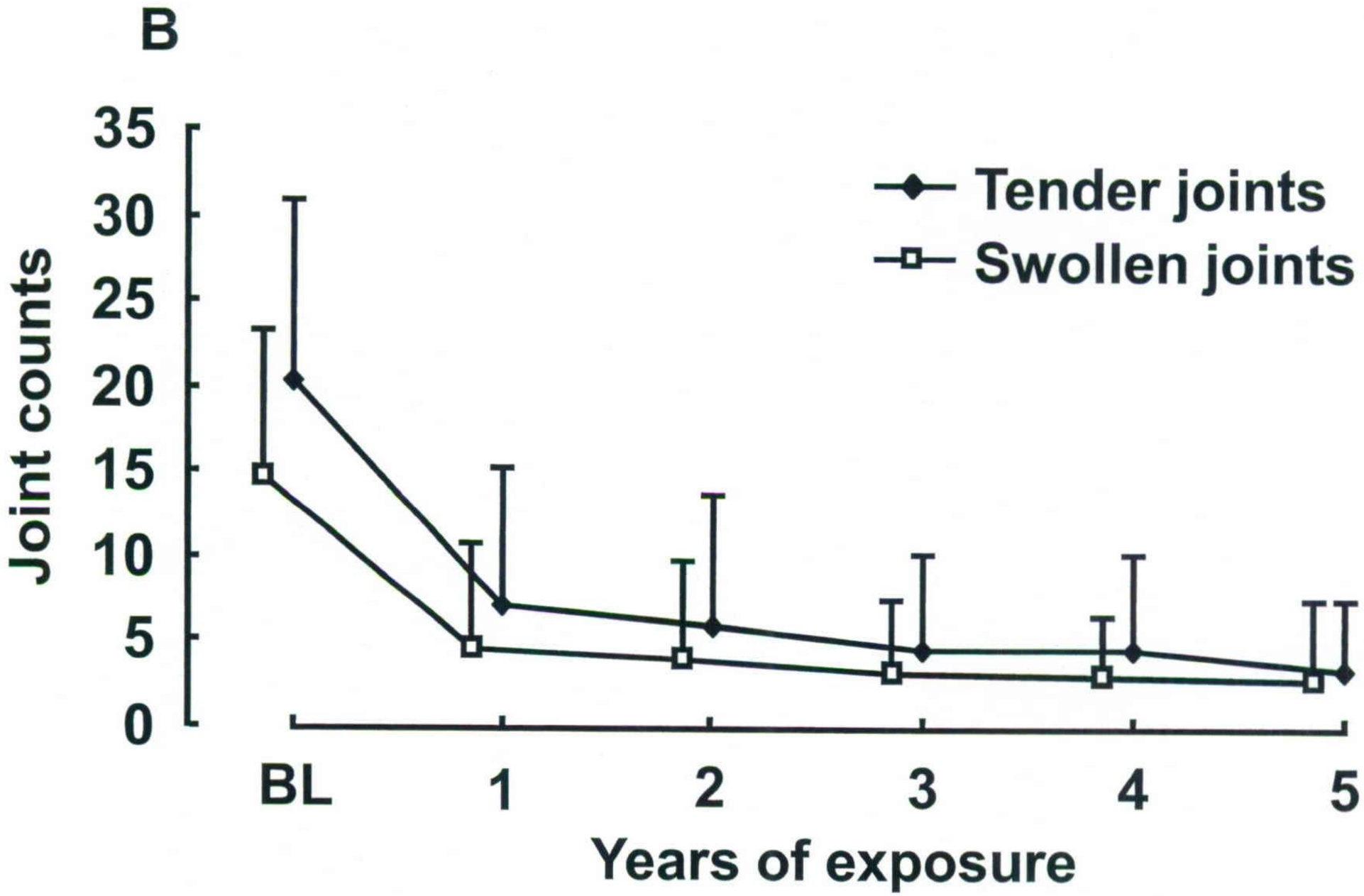

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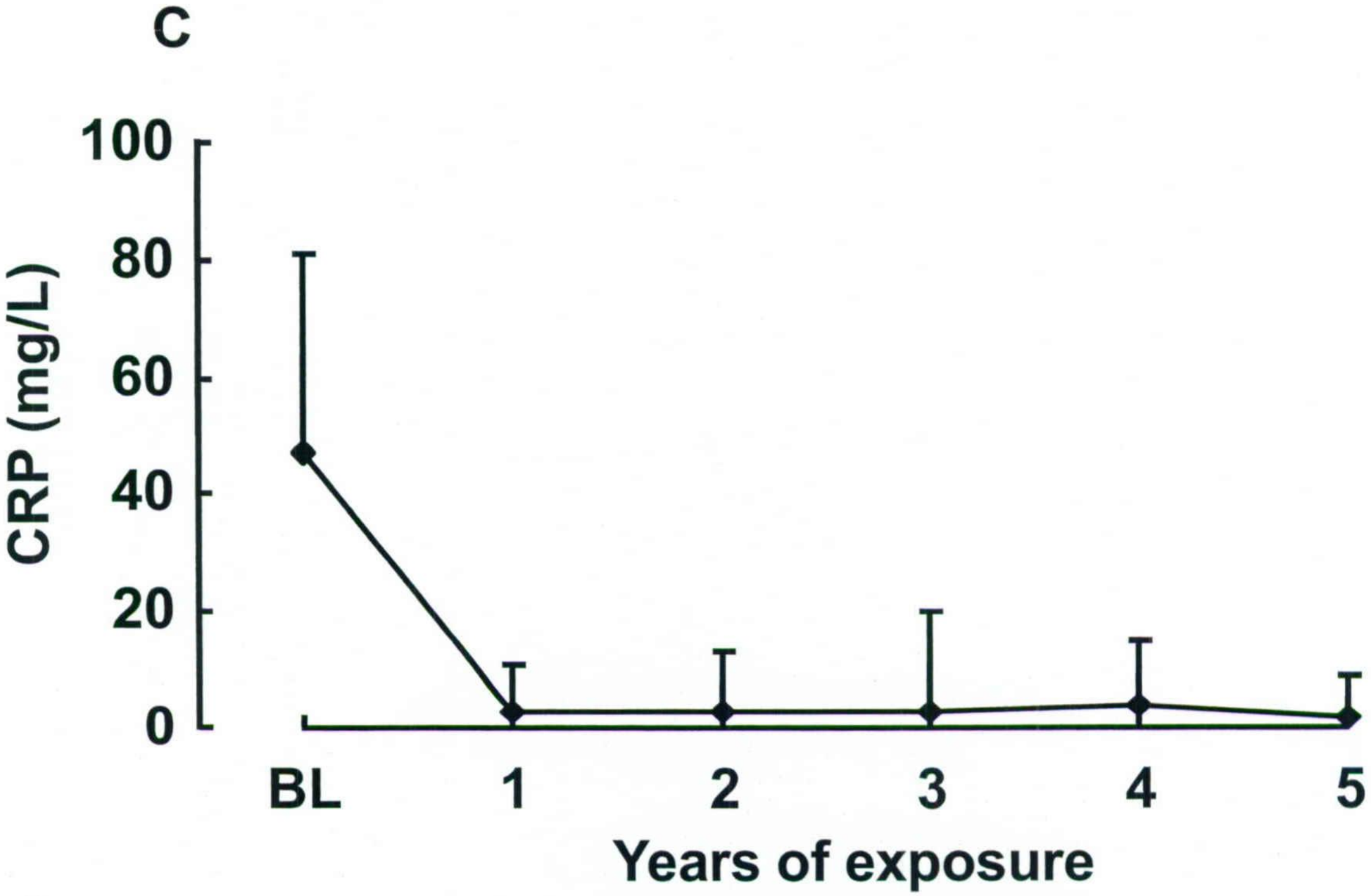

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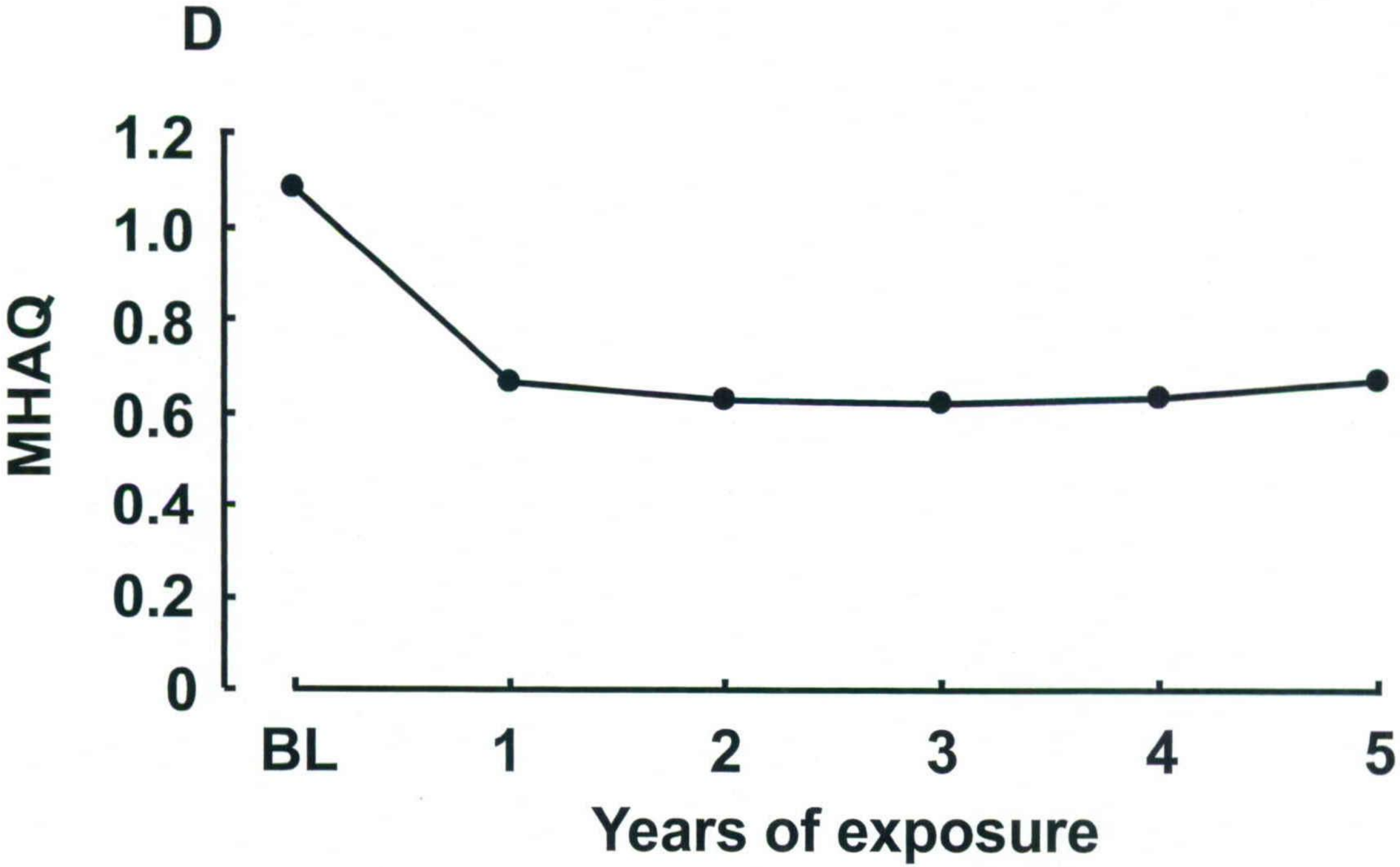

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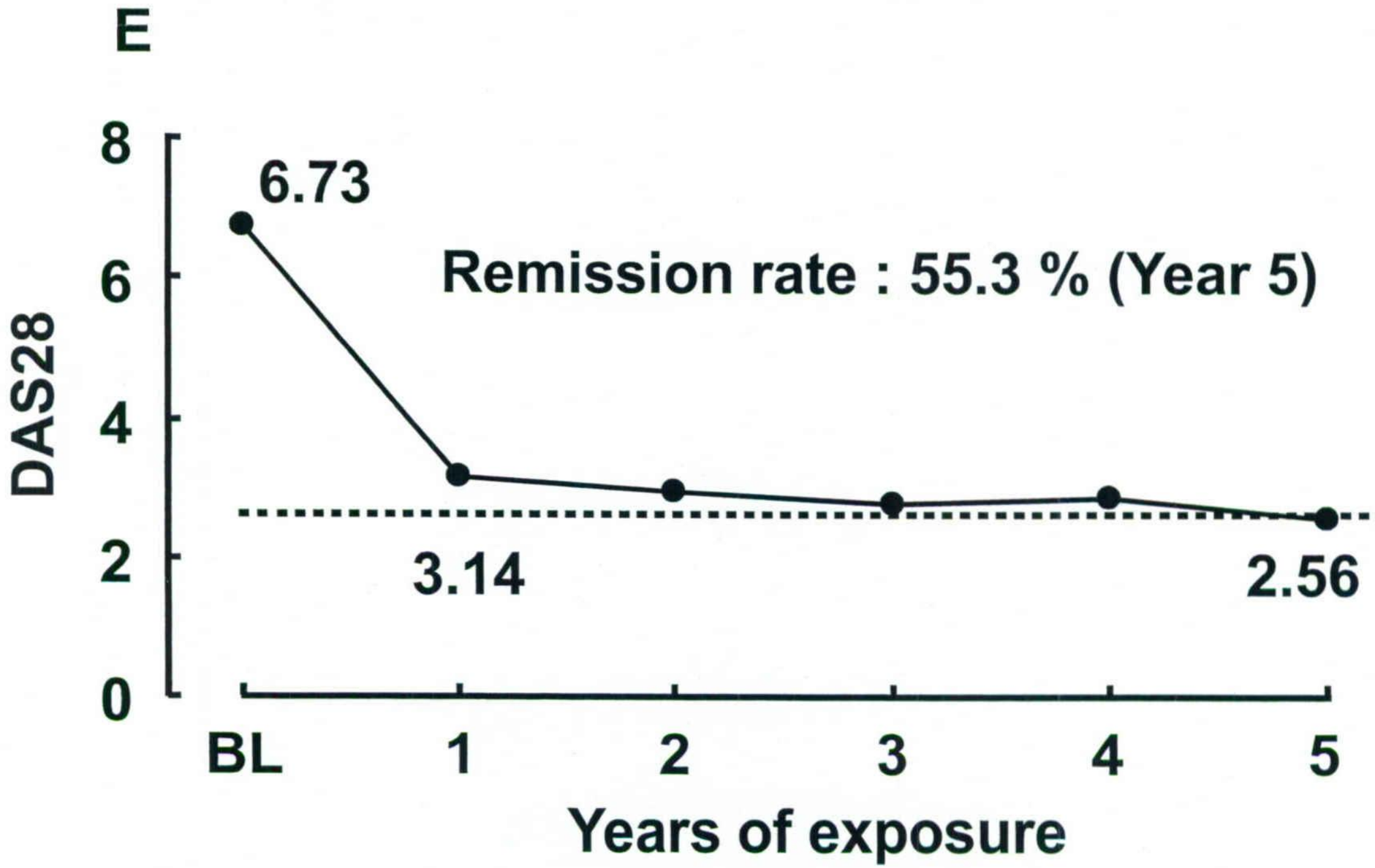

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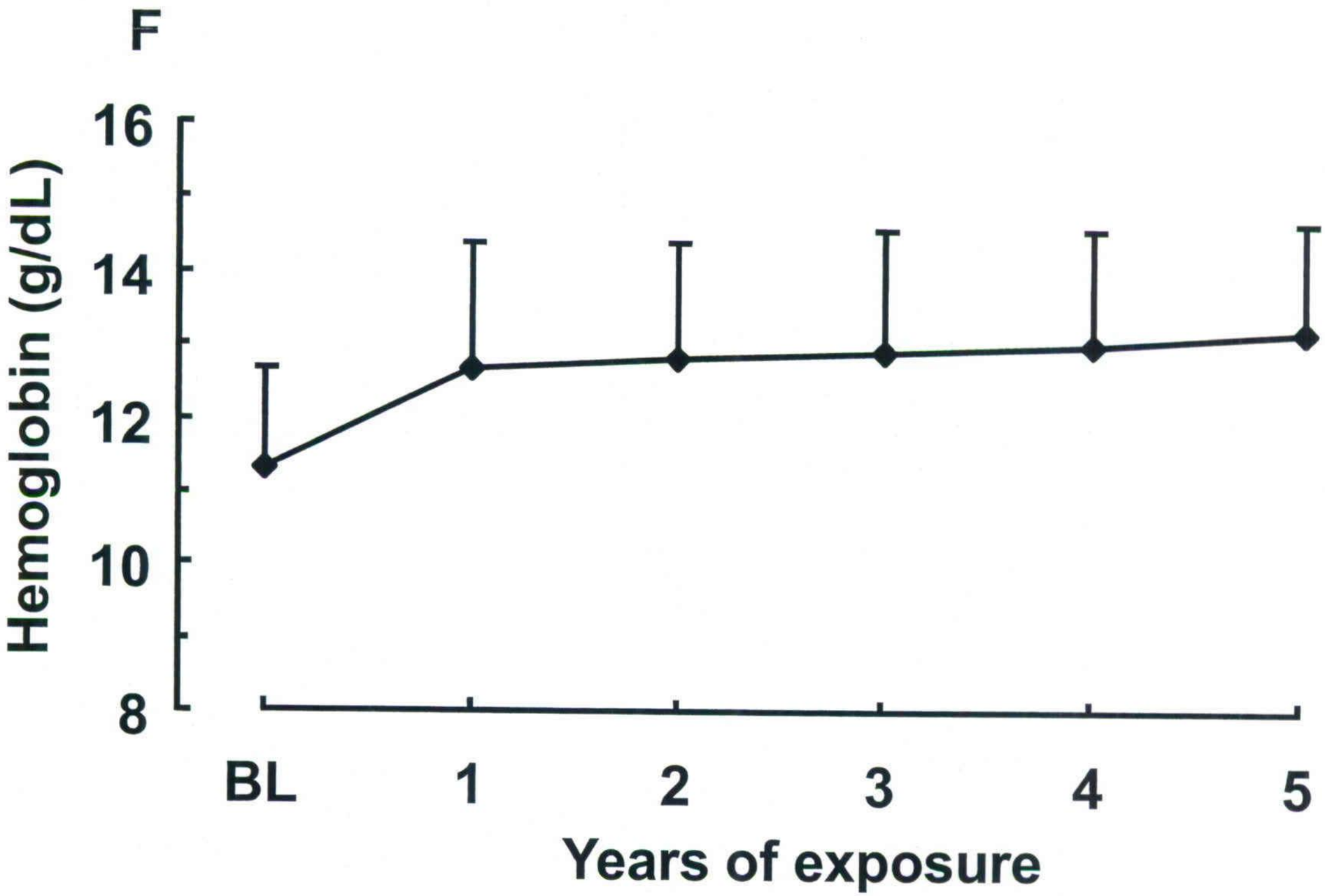

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