A Population-based Study of Morbidity and Mortality in Mannose-binding Lectin Deficiency

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Abstract
Reduced levels of wild-type mannose-binding lectin (MBL) may increase susceptibility for infection, other common diseases, and death. We investigated associations between MBL deficiency and risk of infection, other common diseases, and death during 24, 24, and 8 yr of follow-up, respectively. We genotyped 9,245 individuals from the adult Danish population for three MBL deficiency alleles, $B$, $C$, and $D$, as opposed to the normal noncarrier $A$ allele. Hospitalization incidence per 10,000 person yr was 644 in noncarriers compared with 631 in heterozygotes (log-rank: $P = 0.39$) and 658 in deficiency homozygotes ($P = 0.53$). Death incidence per 10,000 person yr was 235 in noncarriers compared with 244 in heterozygotes ($P = 0.44$) and 274 in deficiency homozygotes ($P = 0.12$). After stratification by specific cause of hospitalization or death, only hospitalization from cardiovascular disorders was increased in deficiency homozygotes versus noncarriers ($P = 0.02$). When retested in two case control studies, this association could not be confirmed. Incidence of hospitalization or death from infections or other serious common disorders did not differ between deficiency homozygotes and noncarriers. In conclusion, in this large study in an ethnically homogenous Caucasian population, there was no evidence for significant differences in infectious disease or mortality in MBL-deficient individuals versus controls. Our results suggest that MBL deficiency is not a major risk factor for morbidity or death in the adult Caucasian population.

Key words: complement • mannan • innate immunity • infection • genetics

Introduction
Infectious diseases are important causes of morbidity and mortality worldwide (1, 2). Our first set of immune responses during infection constitutes the innate immune system. A central player in this system is mannose-binding lectin (MBL), an acute phase protein with the capacity to bind to a broad range of bacteria and vira and subsequently kill them by activating the complement system (3–5). About 5% of Caucasians have an inherited deficiency of MBL leading to reduced plasma levels of wild-type MBL protein (5–7). This may impair normal innate immune function and increase susceptibility for infection (8). Because MBL may also play an important role in other serious common diseases like atherosclerosis (9, 10), chronic pulmonary disease (11, 12), and cancer (13, 14), MBL deficiency could also affect risk of these diseases and mortality.

MBL deficiency is associated with homozygosity for either of the three deficiency alleles of the MBL gene, the $B$, $C$, and $D$ alleles (5–7). These mutant alleles are also designated $O$ alleles as opposed to the normal noncarrier $A$ allele. In previous studies, MBL deficiency has been associated with increased susceptibility for bacterial and viral infections (8), as well as with many other diseases like atherosclerosis (9, 10), leukemia (14), and miscarriage (15). Therefore, and because of the high population frequency of MBL deficiency, this condition could play an important role in public health. However, the significance of MBL deficiency in the adult general population remains rela-
tively unknown because previous studies were mainly based on hospital cases or children (5, 9–25).

We tested the hypothesis that MBL deficiency homozygotes and heterozygotes compared with noncarriers are at increased risk of morbidity and mortality from infectious and other common diseases in the adult general population. For this purpose, we screened 9,245 individuals from the adult Danish population for the B, C, and D MBL deficiency alleles, and associated MBL genotype with risk of infection, other common diseases, and death during median follow-up periods of 24, 24, and 8 yr, respectively.

**Materials and Methods**

All subjects who participated in the 1991–1994 examination of the Copenhagen City Heart Study were included in this population-based study (Fig. 1, top; reference 26). The participants aged 20 yr and above were selected randomly after age stratification into 5-yr age groups from among residents of Copenhagen. Of the 17,180 individuals invited, 10,135 participated, 9,259 gave blood, and 9,245 were genotyped for the B, C, and D deficiency alleles of the MBL gene. Details of study procedures (26–29) and some characteristics of nonresponders (30, 31) are described elsewhere. More than 99% were Caucasians of Danish descent. All participants gave written informed consent, and the ethics committee for Copenhagen and Frederiksberg approved the study (no. 100.2039/91).

Participants at the Copenhagen City Heart Study examination filled out a self-administered questionnaire, which was validated by the participant and an investigator on the day of attendance. Participants reported on smoking habits (current smoker, ex-smoker, or never smoker), weekly physical activity (<2 h light activity, 2–4 h light activity, >4 h light activity, or 2–4 h heavy activity or >4 h heavy activity), and on weekly alcohol consumption. Recent respiratory infection was self-reported (cold, bronchitis, or lung infection) 4 wk before the Copenhagen City Heart Study examination. Blood pressure was measured by trained technicians using a London School of Hygiene Sphygmomanometer on the left arm after 5 min rest with the subject in the sitting position (32). Cholesterol was determined enzymatically by conventional methods (CHOD-PAP; Boehringer). Body mass index was weight divided by height squared. Spirometry-defined chronic obstructive pulmonary disease was FEV₁ < 80% of predicted and FEV₁/FVC < 0.7, excluding self-reported asthma.

Based on the World Health Organization International Classification of Diseases 8th and 10th Editions, additional information on morbidity was drawn from the Danish National Hospital Discharge Register (data from May 1, 1976 to December 31, 2000 was available), whereas data on mortality was drawn from the Danish National Register of Causes of Death (data from April 1, 1992 to December 31, 1999 was available for cause-specific deaths, whereas data for death only was available until December 31, 2001). Of the 1,726 deaths, which occurred in the population sample from 1991 through 2001, 1,065 (62%) had not yet been assigned with a certain death cause in the Danish National Register of Causes of Death. We grouped all diagnoses based on the Global Burden of Disease classification system (1, 2, 33). This paper focuses on groups of disease with high morbidity and mortality in developed countries. Subclassification of the disease groups was performed for endpoints particularly relevant for MBL deficiency.

During 1991 through 1993, we also recruited 947 patients with ischemic heart disease (IHD) referred for coronary angiography at Copenhagen University Hospital. Experienced cardiologists diagnosed IHD on the basis of characteristic symptoms of stable angina pectoris plus at least one of the following: severe stenosis on coronary angiography, myocardial infarction, or a positive result on exercise electrocardiography. We further identified 701 patients with ischemic cerebrovascular disease (ICVD) referred to Copenhagen University Hospital for outpatient ultrasonography of the carotid artery during 1994 through 2001. ICVD was diagnosed on the basis of ischemic stroke, transient ischemic attack, or amaurosis fugax, together with carotid artery stenosis ≥50%. All patients had computed tomography scans performed, and those with cerebral hemorrhage were excluded. All 947 and 701 patients with IHD and ICVD were genotyped. For each of these prevalent cases with ICVD and IHD, two control subjects of the same gender, age (within 1 yr), and smoking status (current smoker, ex-smoker, or never smoker) were randomly selected among Copenhagen City Heart Study participants with-
Table I. Baseline Characteristics of Subjects Sampled from the General Population by MBL Deficiency Genotype

| Noncarriers | Heterozygotes | Homozygotes | P-value\(^a\) |
|-------------|---------------|-------------|---------------|
| Women/Men   | 2,962/2,398   | 1,880/1,502 | 275/228       | 0.91          |
| Age, yr     | 57 ± 0.2      | 58 ± 0.3    | 58 ± 0.7      | 0.41          |
| Current smokers (%) | 2,621 (49)   | 1,624 (48)  | 246 (49)      | 0.82          |
| Systolic blood pressure, mmHg | 138 ± 0.3      | 139 ± 0.4    | 140 ± 1.0      | 0.21          |
| Alcohol consumption, g/wk | 114 ± 2.1      | 113 ± 2.6    | 109 ± 6.7      | 0.61          |
| Plasma cholesterol, mmol/L | 6.1 ± 0.02      | 6.2 ± 0.02    | 6.2 ± 0.06     | 0.13          |
| Body mass index, kg/m\(^2\) | 26 ± 0.2      | 26 ± 0.1    | 26 ± 0.1       | 0.59          |
| Physical inactivity\(^b\) (%) | 664 (13)      | 390 (12)    | 60 (12)        | 0.36          |

Values are number of individuals (%) or mean ± SEM.

\(^a\)P-values by Pearson’s \(\chi^2\)-test, Kruskal Wallis test, or analysis of variance. To approach normal distribution, body mass index was logarithmically transformed before statistical analysis.

\(^b\)Physical inactivity was <2 h of light physical activity per week.

Table II. Morbidity Leading to Hospitalization According to MBL Deficiency Genotype during 24 yr Follow-up

| Incidence | Incidence | RR\(^a\) | RR\(^a\) (95% CI) | P-value\(^b\) | P-value\(^b\) (95% CI) |
|-----------|-----------|----------|-------------------|---------------|------------------------|
| Noncarriers | Heterozygotes | Homozygotes | Any hospitalization | 644 | 1.0 | 631 | 0.39 | 0.98 (0.93–1.0) | 658 | 0.53 | 1.1 (0.96–1.2) |
| Infectious and parasitic diseases | 55 | 1.0 | 57 | 0.58 | 1.1 (0.93–1.2) | 50 | 0.48 | 0.91 (0.69–1.2) |
| Respiratory infections | 42 | 1.0 | 37 | 0.09 | 0.88 (0.76–1.0) | 40 | 0.75 | 0.96 (0.71–1.3) |
| Respiratory disorders | 51 | 1.0 | 49 | 0.53 | 0.99 (0.87–1.1) | 61 | 0.13 | 1.2 (0.97–1.6) |
| Cardiovascular disorders | 136 | 1.0 | 132 | 0.38 | 0.95 (0.87–1.0) | 162 | 0.02 | 1.2 (1.0–1.4) |
| Malignant neoplasms | 61 | 1.0 | 62 | 0.77 | 1.0 (0.90–1.1) | 65 | 0.64 | 1.0 (0.81–1.3) |
| Digestive disorders | 118 | 1.0 | 112 | 0.20 | 0.95 (0.87–1.0) | 135 | 0.10 | 1.2 (0.98–1.4) |
| Musculoskeletal disorders | 140 | 1.0 | 135 | 0.28 | 0.96 (0.89–1.0) | 140 | 0.96 | 1.0 (0.88–1.2) |
| Neuropsychiatric disorders | 57 | 1.0 | 57 | 0.85 | 0.97 (0.89–1.1) | 53 | 0.61 | 0.93 (0.71–1.2) |

\(^a\)Relative risks (RR) were adjusted for gender, age, smoking habits, systolic blood pressure, alcohol, cholesterol, body mass index, and physical inactivity.

\(^b\)P-values by log-rank test. Infectious and parasitic diseases: 001–136, 320, 323, 612–614, 620, 622, A00–B99, G00, G03–G04, N70–N73; respiratory infections: 460–486, 381–382, J00–J06, J10–J18, J20–J22, H65–H66; respiratory disorders: 490–519, J30–J39; cardiovascular disorders: 390–488, I00–I99; malignant neoplasms: 140–209, C00–C97; digestive disorders: 530–577, K20–K92; musculoskeletal disorders: 710–738, M00–M99; neuropsychiatric disorders: 290–315, 321–322, 324–358, F01–F99, G06–G98.
log-rank test (27–29). Cox regression analysis with forced entry examined time to disease or death by using hazard ratios (relative risks) and 95% confidence intervals (CIs). The model adjusted for gender, age (deciles), smoking habits (current smoker, ex-smoker, and never smoker), systolic blood pressure (deciles), alcohol consumption (nonusers and deciles), plasma cholesterol (deciles), body mass index (deciles), and physical activity (2 h light activity weekly, 2–4 h light activity, 4 h light activity, or 2–4 h heavy activity or 4 h heavy activity weekly). Unadjusted conditional logistic regression estimated odds ratios in matched case control studies 1 and 2 (Fig. 1, bottom).

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The sponsors of the study are public or nonprofit organizations and support science in general. They had no role in gathering, analyzing, or interpreting the data and could neither approve nor disapprove the submitted manuscript.

### Results

**MBL genotype frequencies in this sample from the Danish general population were 58% for \(A/A\) noncarriers, 37% for \(A/O\) heterozygotes, and 5% for \(O/O\) deficiency homozygotes.** Frequencies for the \(B\), \(C\), and \(D\) alleles were 0.145, 0.017, and 0.076, respectively. Genotype frequencies did not differ from those predicted by the Hardy-Weinberg equilibrium (\(\chi^2\)-test for \(B\) allele: \(P = 0.75\); \(C\) allele: \(P = 0.29\); \(D\) allele: \(P = 0.87\)). Distribution of baseline characteristics in this population did not differ between individuals with the three different genotypes (Table I).

**Morbidity.** Incidence of any hospitalization per 10,000 person \(\cdot\) yr was 644 in noncarriers compared with 631 in heterozygotes (log-rank: \(P = 0.39\)) and 658 in deficiency homozygotes (\(P = 0.53\); Table II). After adjustment for gender, age, smoking habits, systolic blood pressure, alcohol consumption, cholesterol level, body mass index, and physical activity, the relative risks for any hospitalization were not significantly different from 1.0 in heterozygotes or deficiency homozygotes compared with noncarriers.

### Table III. Morbidity Leading to Hospitalization According to MBL Deficiency Genotype during 24 yr Follow-up

|                       | Noncarriers | Heterozygotes | Homozygotes |
|-----------------------|-------------|---------------|-------------|
|                       | Incidence N/10,000 person \(\cdot\) yr | RR\(^a\) | P-value\(^b\) | Incidence N/10,000 person \(\cdot\) yr | RR\(^a\) | P-value\(^b\) | Incidence N/10,000 person \(\cdot\) yr | RR\(^a\) | P-value\(^b\) |
| **Infectious diseases** |             |               |             |             |             |             |             |             |             |
| Meningitis            | 0.91        | 1.0           | 1.1         | 0.69        | 0.99 (0.39–2.5) | 0           | —           | —           | —           |
| HIV/AIDS              | 0.68        | 1.0           | 0.60        | 0.82        | 0.75 (0.23–2.5) | 0           | —           | —           | —           |
| Tuberculosis          | 16          | 1.0           | 18          | 0.45        | 1.1 (0.88–1.4) | 20          | 0.37        | 1.2 (0.80–1.9) |
| Pneumonia             | 29          | 1.0           | 25          | 0.18        | 0.89 (0.75–1.1) | 32          | 0.47        | 1.1 (0.82–1.6) |
| Skin infection        | 9.9         | 1.0           | 9.7         | 0.90        | 1.0 (0.77–1.4) | 12          | 0.41        | 1.2 (0.78–2.3) |
| Hepatitis             | 1.7         | 1.0           | 1.4         | 0.68        | 0.86 (0.42–1.7) | 0.81        | 0.47        | 0.49 (0.07–3.7) |
| Diarrhoeal diseases   | 7.9         | 1.0           | 8.3         | 0.74        | 1.1 (0.81–1.5) | 9.8         | 0.49        | 1.2 (0.68–2.3) |
| Cystitis              | 16          | 1.0           | 13          | 0.14        | 0.85 (0.67–1.1) | 9.8         | 0.10        | 0.57 (0.32–1.0) |
| Pyelonephritis        | 3.6         | 1.0           | 3.9         | 0.74        | 1.1 (0.67–1.7) | 5.7         | 0.24        | 1.7 (0.78–3.9) |
| **Respiratory disorders** |             |               |             |             |             |             |             |             |             |
| COPD                  | 21          | 1.0           | 22          | 0.85        | 1.1 (0.87–1.3) | 29          | 0.10        | 1.4 (0.97–2.0) |
| Asthma                | 8.9         | 1.0           | 8.2         | 0.59        | 0.89 (0.75–1.1) | 8.1         | 0.77        | 1.1 (0.82–1.6) |
| **Cardiovascular disorders** |         |               |             |             |             |             |             |             |             |
| IHD                   | 43          | 1.0           | 46          | 0.30        | 1.1 (0.94–1.2) | 53          | 0.09        | 1.2 (0.92–1.6) |
| ICVD                  | 21          | 1.0           | 20          | 0.65        | 0.97 (0.80–1.2) | 28          | 0.10        | 1.2 (0.84–1.7) |
| **Maternal conditions** |             |               |             |             |             |             |             |             |             |
| Miscarriage           | 7.2         | 1.0           | 5.7         | 0.19        | 0.89 (0.62–1.3) | 11          | 0.10        | 1.7 (0.96–3.1) |

\(^a\)Relative risks (RR) were adjusted for age, gender, smoking habits, systolic blood pressure, alcohol, cholesterol, body mass index, and physical inactivity.

\(^b\)P-values by log-rank test. Meningitis: 320, G00–G03; HIV/AIDS: 137, B20–B24; tuberculosis: 010–019, A15–A19, B90; pneumonia: 480–486, J12–J18; skin infection: 680–686, L00–L08; hepatitis: 070, B15–B19; diarrhoeal diseases: 000–001,004–006, 008–009, A00–A01, A03–A04, A06–A09; cystitis: 595, N30; pyelonephritis: 590, N10–N12; chronic obstructive pulmonary disease (COPD): 490–492, J41–J44; asthma: 493, J45–J46; IHD: 410–414, I20–I25; ICVD: 430–438, I60–I69; miscarriage: 643, O03.
for cardiovascular disorders after adjustment for potential confounders in heterozygotes and homozygotes compared with noncarriers were 0.95 (95% CI: 0.87–1.0) and 1.2 (1.0–1.4), respectively. This finding was retested in case control studies matched for gender, age, and smoking habits. Odds ratios for ICVD, IHD, or either of these diseases in deficiency homozygotes versus noncarriers were 0.82 (0.53–1.3), 1.1 (0.76–1.5), and 1.1 (0.81–1.4), respectively (not depicted). Incidence of hospitalization from infection or other common diseases did not differ between MBL genotypes (Table II).

After further stratification by specific hospitalization cause, there were trends toward decreased incidence of cystitis and increased incidence of chronic obstructive pulmonary disease, IHD, ICVD, and miscarriage in MBL deficiency homozygotes versus noncarriers (Table III). However, there were no significant changes in risk.

Cross-sectionally, prevalence of recent respiratory infection was 26% in noncarriers compared with 25% in homozygotes (χ²: P = 0.72) and 28% in deficiency homozygotes (P = 0.21; not depicted). Prevalence of spirometry-defined chronic obstructive pulmonary disease was 8.5% in noncarriers compared with 9.4% in homozygotes (P = 0.19) and 11% in homozygotes (P = 0.14; not depicted).

When B, C, and D deficiency alleles were looked at separately versus noncarrier A alleles, none of the heterozygotes, compound heterozygotes, or homozygotes were associated with incidence of any hospitalization (Table IV). Compared with A/A noncarriers, A/D heterozygotes were associated with reduced risk of respiratory infection, A/C heterozygotes with reduced risk of cardiovascular disorders, B/D compound heterozygotes with increased risk of respiratory and digestive disorders, whereas D/D homozygotes were associated with increased risk of digestive disorders. If correction for multiple comparison is performed, all of these five significant associations become nonsignificant. Therefore, and because none of the significant findings are biologically plausible, these findings are likely due to chance alone rather than representing real phenomena. The remaining 65 calculated relative risks were not significant.

**Mortality.** Incidence of death from any cause per 10,000 person · yr was 235 in noncarriers compared with 244 in heterozygotes (log-rank: P = 0.44) and 274 in deficiency homozygotes (P = 0.12; Table V). After adjustment for gender, age, smoking habits, systolic blood pressure, alcohol consumption, cholesterol level, body mass index, and physical activity, relative risks for death were not significantly different from 1.0 in heterozygotes or homozygotes compared with noncarriers.

After stratification by major causes of death (2), mortality from cardiovascular disorders per 10,000 person · yr was 41 in noncarriers compared with 31 in heterozygotes (P = 0.04) and 49 in deficiency homozygotes (P = 0.44; Table V). After adjustment for potential confounders, relative risks for death from cardiovascular disorders in heterozygotes and homozygotes compared with noncarriers were 0.73 (95% CI: 0.55–0.95) and 1.1 (0.70–1.8), respectively. Incidence of death from infection or other common diseases did not differ between MBL genotypes.

When B, C, and D deficiency alleles were looked at separately versus noncarrier A alleles, B/B homozygotes were associated with increased incidence of death from any cause (Table VI). None of the heterozygotes, compound heterozygotes, or other homozygotes were associated with incidence of death from any cause. Compared with A/A noncarriers, A/B heterozygotes were associated with reduced risk of death from cardiovascular disorders. If correction for multiple comparison is performed, both significant associations become nonsignificant. Therefore, these findings are likely due to chance alone rather than representing real phenomena. The remaining 41 calculated relative risks were not significant.

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**Table IV.** Morbidity Leading to Hospitalization According to MBL Deficiency Genotype during 24 yr Follow-up

|                  | Heterozygotes | Compound heterozygotes or homozygotes |
|------------------|--------------|--------------------------------------|
|                  | A/B          | A/D                                   | A/C                                   | B/B | B/D | D/D | B/C | D/C |
| Any hospitalization | 1.0 (0.95–1.1) | 0.93 (0.86–1.0) | 0.98 (0.85–1.1) | 1.0 (0.88–1.2) | 1.1 (0.97–1.3) | 1.1 (0.81–1.5) | 1.0 (0.73–1.4) | 0.81 (0.52–1.3) |
| Infectious and parasitic diseases | 1.1 (0.94–1.3) | 0.98 (0.81–1.2) | 1.1 (0.81–1.6) | 0.74 (0.46–1.2) | 1.1 (0.72–1.6) | 1.2 (0.60–2.4) | 0.90 (0.37–2.2) | 0.28 (0.04–2.0) |
| Respiratory infections | 0.93 (0.78–1.1) | 0.74 (0.58–0.94) | 1.0 (0.67–1.5) | 0.94 (0.59–1.5) | 1.2 (0.80–1.9) | 0.43 (0.11–1.7) | 0.67 (0.21–2.1) | 0.80 (0.20–3.2) |
| Respiratory disorders | 1.1 (0.93–1.2) | 0.89 (0.73–1.1) | 0.77 (0.51–1.2) | 1.2 (0.82–1.8) | 1.7 (1.2–2.4) | 0.67 (0.25–1.8) | 0.96 (0.40–2.3) | — |
| Cardiovascular disorders | 0.96 (0.87–1.1) | 0.98 (0.87–1.1) | 0.77 (0.60–0.99) | 1.3 (0.97–1.6) | 1.2 (0.93–1.5) | 1.4 (0.91–2.3) | 1.3 (0.78–2.1) | 0.44 (0.16–1.2) |
| Malignant neoplasms | 1.0 (0.90–1.2) | 0.94 (0.78–1.1) | 1.2 (0.88–1.6) | 1.1 (0.78–1.6) | 0.93 (0.63–1.4) | 0.82 (0.37–1.8) | 1.4 (0.73–2.7) | 0.79 (0.25–2.5) |
| Digestive disorders | 0.96 (0.87–1.1) | 0.95 (0.83–1.1) | 0.84 (0.64–1.1) | 1.1 (0.80–1.4) | 1.4 (1.1–1.8) | 1.6 (1.0–2.5) | 0.98 (0.54–1.8) | 0.26 (0.07–1.1) |
| Musculoskeletal disorders | 0.95 (0.86–1.0) | 0.96 (0.85–1.1) | 1.0 (0.83–1.3) | 0.96 (0.73–1.3) | 1.1 (0.88–1.5) | 0.95 (0.57–1.6) | 1.0 (0.59–1.8) | 1.1 (0.58–2.2) |
| Neuropsychiatric disorders | 0.96 (0.83–1.1) | 0.99 (0.82–1.2) | 0.93 (0.65–1.3) | 0.94 (0.61–1.4) | 1.2 (0.84–1.7) | 0.43 (0.14–1.3) | 0.86 (0.35–2.1) | — |

Values are relative risks (95% CI). Relative risks were adjusted for gender, age, smoking habits, systolic blood pressure, alcohol, cholesterol, body mass index, and physical inactivity. The A/A genotype was used as reference group.

The D/C genotype also included each of the following: C/C, B/B/D, B/B/C, and B/D/D.

P < 0.05 by Wald statistic. Infectious and parasitic diseases: 001–136, 320, 323, 612–614, 620, 622, A00–B99, G00, G03–G04, N70–N73; respiratory infections: 460–486, 381–382, J00–J06, J10–J18, J20–J22, H60–H66; respiratory disorders: 490–519, J30–J98; cardiovascular disorders: 390–458, I00–I99; malignant neoplasms: 140–209, C00–C97; digestive disorders: 530–577, K20–K92; musculoskeletal disorders: 710–738, M00–M99; neuropsychiatric disorders: 290–315, 321–322, 324–358, F01–F99, G06–G98.
In this large study in an ethnically homogenous Caucasian population, there was no evidence for differences in infectious disease or mortality in MBL-deficient individuals versus controls. Our results suggest that MBL deficiency is not a major risk factor for morbidity or death in the adult Caucasian population. These observations were independent of major risk factors for morbidity and mortality (35) such as gender, age, smoking, blood pressure, alcohol consumption, cholesterol level, body mass index, and physical inactivity.

Because ~5% of Caucasians are MBL deficient, it is indeed important that these individuals are relatively unaffected by the deficiency. MBL replacement therapy is currently being evaluated (36–39). However, because MBL-deficient individuals do not differ in morbidity or mortality from noncarriers in this study, MBL reconstitution therapy does not appear to be of relevance for the average Caucasian MBL-deficient adult. Certainly, MBL replacement therapy might be warranted in the future, if randomized clinical trials can demonstrate improved clinical health status in certain patient subgroups with MBL deficiency. Today, however, diagnosing MBL deficiency among adults should not alter management because predicted long-term morbidity and mortality appear unaffected in these individuals.

Even though it is generally accepted that MBL is a central factor in the innate immune system (5), MBL deficiency did not increase risk for infection, other serious common diseases, or death in this study. This indicates that other immune systems, e.g., ficolins (5, 40), are able to take over MBL function in most adults with MBL deficiency. In concordance, MBL deficiency may only come into play when other parts of the immune system are compromised, e.g., by chemotherapy as shown in some (24, 41) but not all previous studies (42). MBL deficiency has been associated with increased risk for severe and recurrent infections, but almost solely in hospital-based studies (8). As opposed to this, our results suggest that most adults with MBL deficiency in the general population are asymptomatic. Thus, it appears that MBL deficiency may only increase risk of infection in certain contexts or subgroups of patients, or when additional impairments of the immune system are present (5).

Previous studies have shown an association between MBL deficiency and accelerated progression of atherosclerosis (9, 10, 43). This may lead to a higher incidence of cardiovascular disease as observed in this study. This finding, however, could not be confirmed in the matched case control studies in our study. Also, the number of deaths from cardiovascular disorders was not increased by MBL deficiency. Because of this, and because the risk estimate of 1.2 for cardiovascular disease was relatively small, we believe that MBL deficiency is of no greater clinical importance in cardiovascular disease. It cannot be ruled out, however, that MBL deficiency in certain contexts (44) or subgroups of patients may increase the risk of cardiovascular disease significantly.

A population-based study of 252 children found that MBL deficiency was associated with a twofold risk for acute respiratory tract infection (17). In our study during adulthood, MBL deficiency did not increase risk of respiratory infection outcomes on a population basis. Thus, it is possible...
Respiratory disorders 0.67 (0.38–1.2) 0.74 (0.33–1.6) 1.2 (0.36–3.8) 2.2 (0.77–6.3) 1.0 (0.24–4.3) 2.3 (0.30–17) — —

Respiratory infections 0.56 (0.19–1.7) 0.73 (0.20–2.7) 1.1 (0.14–8.8) — 0.93 (0.09–9.2) — — —

Infectious and parasitic diseases 2.4 (0.85–7.0) — — 3.2 (0.34–31) — — —

Table VI. Mortality According to MBL Deficiency Genotype during 8 Year Follow-up

| Genotype | A/B | A/D | A/C | B/B | B/D | D/D | B/C | D/C |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|
| Death from any cause | 1.1 (0.93–1.2) | 1.0 (0.88–1.2) | 1.1 (0.83–1.5) | 1.4 (1.0–1.9) | 0.96 (0.60–1.3) | 0.61 (0.27–1.4) | 0.98 (0.51–1.9) | 0.72 (0.29–1.7) |
| Infectious and parasitic diseases | 2.4 (0.85–7.0) | — | — | 3.2 (0.34–31) | — | — | — | — |
| Respiratory infections | 0.56 (0.19–1.7) | 0.73 (0.20–2.7) | 1.1 (0.14–8.8) | — | 0.93 (0.09–9.2) | — | — | — |
| Respiratory disorders | 0.67 (0.38–1.2) | 0.74 (0.33–1.6) | 1.2 (0.36–3.8) | 2.2 (0.77–6.3) | 1.0 (0.24–4.3) | 2.3 (0.30–17) | — | — |
| Cardiovascular disorders | 0.72 (0.52–0.99) | 0.76 (0.50–1.2) | 0.65 (0.27–1.6) | 1.7 (0.89–3.2) | 0.77 (0.31–1.9) | 1.2 (0.28–4.7) | 0.60 (0.08–4.3) | 0.95 (0.13–7.0) |
| Malignant neoplasms | 1.1 (0.87–1.4) | 1.2 (0.85–1.6) | 0.90 (0.49–1.7) | 1.4 (0.76–2.4) | 1.2 (0.65–2.2) | 0.89 (0.22–3.6) | 1.9 (0.69–5.1) | 0.84 (0.12–6.0) |
| Digestive disorders | 1.0 (0.38–2.7) | 0.95 (0.83–1.1) | — | 1.3 (0.17–9.5) | 0.69 (0.09–6.5) | — | — | — |
| Musculoskeletal disorders | — | — | — | — | — | — | — | — |
| Neuropsychiatric disorders | 1.8 (0.69–4.8) | 0.42 (0.05–3.3) | 2.8 (0.34–23) | — | — | — | — | — |

Values are relative risks (95% CI). Relative risks were adjusted for gender, age, smoking habits, systolic blood pressure, alcohol, cholesterol, body mass index, and physical inactivity.

The A/A genotype was used as a reference group.

The D/C genotype also included each of the following: C/C, B/B/D, B/B/C, B/D/D.

P < 0.05 by Wald statistics. Infectious and parasitic diseases: 001–136, 320, 323, 612–614, 620, 622, A00–B99, G00, G03–G04, N70–N73; respiratory infections: 460–486, 381–382, J00–J06, J10–J18, J20–J22, H65–H66; respiratory disorders: 490–519, J30–J99; cardiovascular disorders: 390–458, I00–I99; malignant neoplasms: 140–209, C00–C97; digestive disorders: 530–577, K20–K99; musculoskeletal disorders: 710–738, M00–M99; neuropsychiatric disorders: 290–315, 321–322, 324–358, F01–F99, G06–G08.

ble that MBL deficiency could play a role in pulmonary host defense in children during the vulnerable period when the adaptive immune system is immature (17), while not having an effect in adults. It is also possible that risk of respiratory infection is increased by MBL deficiency in children of Inuit origin only (17), whereas risk is unaffected in children (45) and adults in Caucasian populations.

Normal levels of MBL or wild-type genotype have also been associated with higher incidence of disease by mycobacteria, indicating an advantage of the host in situations where opsonophagocytosis might be detrimental (46, 47). We were not able to support these previous observations. However, in contrast to this study, the former studies used different study designs or were performed in populations where incidence for mycobacteria-associated disease is high (17), while not having an effect in adults. It is also possible that risk of respiratory infection is increased by MBL deficiency in children of Inuit origin only (17), whereas risk is unaffected in children (45) and adults in Caucasian populations.

Participants were genotyped only if they attended the 1991–1994 examination of the Copenhagen City Heart Study. A selection bias may have occurred if death or morbidity prevented certain individuals from being genotyped. However, there are several arguments against such bias: (a) the observed MBL genotype distribution did not differ from that predicted by the Hardy–Weinberg equilibrium, (b) MBL genotype distribution observed in the Copenhagen City Heart Study was similar to that observed in other Caucasian populations (5), and (c) limiting the analyses to a follow-up period after the 1991–1994 examination yielded results similar to those presented. It should be noted that if one insists on only looking at results after correction for multiple comparisons, MBL genotype was not significantly associated with cardiovascular disease. As we studied a sample of the caucasian Danish general population, generalizability of our data to other races and to less affluent parts of the world may potentially be constrained. Bias caused by investigators’ knowledge of disease or risk factor status seems unlikely because we selected from a general population and genotyped our sample without knowledge of disease status. Misclassification of genotypes seems unlikely because the diagnosis of the B and D alleles included a control site for restriction enzyme digestion, and because all subjects with the MBL deficiency genotype were reanalyzed to confirm the diagnosis.

In conclusion, we found no evidence for differences in infectious disease or mortality in MBL-deficient individuals versus controls. Our results suggest that MBL deficiency is not a major risk factor for infection, other serious common diseases, or death in the adult Caucasian population. These are important findings because MBL replacement therapy is currently under evaluation (36–39).

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