

## Review

# Burden of illness of diabetic macular edema: literature review

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## Abstract

### Objective:

To provide an overview of the literature on the burden of diabetic macular edema (DME) in the United States and selected European countries.

### Research design and methods:

Computerized searches of English-language literature were conducted in PubMed/MEDLINE (1980–2009). The searches were supplemented with electronic and manual searches of relevant society/association proceedings and bibliographies of electronically identified sources. Abstracts were reviewed for relevance to any of the following topics: epidemiology, including prevalence and incidence; health outcomes; resource use and treatment patterns; and economic and humanistic burden associated with DME. Relevant full text articles were retrieved and major findings were synthesized and compared within and across countries.

### Results:

A total of 400 citations were included in the initial review. After abstract screening, 47 articles were deemed pertinent and summarized in this review. The prevalence of DME among diabetic patients ranged from 0.85% to 12.3% across the countries studied. The prevalence and incidence of DME vary depending on type of diabetes (1 vs. 2), insulin- vs. non-insulin-dependence, and duration of disease (years since diagnosis). Although literature findings are limited and indicate a need for further investigation, a synthesis of the available results indicates that DME has a negative impact on patients' health-related quality of life. In addition, patients with DME consume significantly more healthcare resources and incur higher costs compared to diabetic patients without retinal complications.

### Conclusions:

There remains a need for consistent data capture and assessment within and between countries included in this analysis. Despite the limited evidence, DME appears to be a costly disease that has a negative impact on patients' quality of life.

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### Key words:

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## Introduction

Diabetic macular edema (DME) is an ocular complication of diabetes mellitus (type 1 and 2). Diabetes may cause capillaries in the eye to become abnormally permeable and leak fluid into the retinal tissue of the macula, causing DME. This can result in vision loss and eventual blindness if left untreated. Laser photocoagulation is the standard of treatment for DME. Other treatments such as intra-ocular corticosteroids and anti-vascular endothelial growth factor (VEGF) are showing promise in treating DME<sup>1</sup>.

The burden of DME is likely to increase as the prevalence of diabetes is expected to rise by more than 50% globally from 2000 to 2030, with the number of diabetes cases estimated to reach 300 million worldwide by 2025<sup>2,3</sup>.

In the US alone, diabetes affects an estimated 23.6 million people, or 8% of the US population. Diabetes is the leading cause of new cases of blindness among adults aged 20–74 years, with a projected 12 000–24 000 new cases of blindness in these adults each year in the US<sup>4</sup>. At the baseline examination in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of the diabetic patients diagnosed before the age of 30 and 1.6% of patients diagnosed after the age of 30 were legally blind (visual acuity 20/200 or worse in the better eye)<sup>5</sup>. Although the percentage of cases of blindness in these patients actually attributable to DME is unknown, the negative impact of DME on vision remains a serious concern among the diabetic population.

In the past few decades, there have been advances in medical therapies and increased emphasis on lifestyle modification to control hyperglycemia and hypertension; patients have been increasingly offered diabetes education and regular screening; and scientists and clinicians are continuing to develop new treatments and procedures to allow early detection and slow progression of DME. To what extent, if any, these improvements lead to declines in the prevalence and incidence of DME in developed countries remains unknown. In a cost-containing environment, besides assessing the effectiveness of existing or new treatments for DME, it is important to understand the disease burden, how DME is currently treated in each country, and the financial implications of these interventions to the country and its healthcare system's budget. Therefore, the purpose of this report is to review the studies performed to date that assess the burden of DME, which includes epidemiology (prevalence and incidence of DME or clinically significant DME [CSDME] as defined in the Early Treatment Diabetic Retinopathy Study [ETDRS])<sup>6</sup>, health outcomes or functional impairment, the economic burden, and the impact of DME and/or visual impairment (VI) on patients' health related quality of life (HRQoL).

## Methods

Systematic computerized literature searches were conducted in PubMed/MEDLINE using the following search terms: 'diabetic macular edema,' 'macular edema' in combination with the following terms: 'prevalence,' 'incidence,' 'visual impairment,' 'blindness,' 'burden,' 'economics or cost,' 'utilization,' 'quality of life or QOL,' and 'utility.' The search was limited to human studies published in English from January 1980 to October 2009.

According to International Diabetes Federation, more than 80% of the estimated global expenditures on diabetes are made in the world's economically richest countries. Therefore, 12 countries were selected with the highest health expenditure for diabetes that represent both Western and Northern Europe (the United Kingdom

[UK], Germany, France, Sweden, Norway, Finland, Denmark, Italy, Spain, Belgium, Portugal, the Netherlands) and the US as the focus of this review.

Based upon an initial abstract review, articles pertaining to the topics of interest in the relevant countries were selected for full-text review. After a detailed review, original articles with findings pertaining specifically to DME or CSDME were included and summarized in this literature review. The literature search was also supplemented with electronic and manual searches of relevant society/association proceedings on the same topics from 2005 to 2009 and a manual search of bibliographies from the identified sources.

It should be noted that topics associated with risk factors, staging and screening for the disease, burden of diabetic retinopathy in general, and information reported outside of the 13 pre-specified countries were not included in this review. Editorials, letters, review articles, original reports describing biochemical and pathogenic mechanisms, and cost-effectiveness studies of treatments were also excluded from the initial abstract review.

## Results

The initial PubMed/MEDLINE search generated over 400 citations. Based upon an initial review of the abstracts, 189 were considered relevant and 145 full-text articles were retrieved (44 articles were not available from the library or electronic source). Electronic and manual searches of relevant society/association proceedings and a manual bibliography search generated an additional 35 citations for consideration. Out of the 180 references, 133 were excluded since they were not designed to describe incidence/prevalence/burden of DME or CSDME in the selected countries. The remaining articles were included for the final review and summary.

## Prevalence

Prevalence is usually measured by either point prevalence or lifetime prevalence. Point prevalence is the proportion of individuals affected by some condition out of a particular population at one moment in time. Lifetime prevalence is the proportion of a particular population who has a history of some condition at one point in time. Most publications that measured the prevalence of DME or CSDME provided point prevalence for different populations of diabetes (type 1, type 2 or mixed). Although the reported prevalence of diabetic retinopathy among patients with newly diagnosed diabetes ranged from 0 to 30%<sup>7</sup>, no information existed on the prevalence of DME in these cases. Studies that were not confined to newly diagnosed diabetes found that the prevalence of DME (including CSDME) was strongly correlated with the type of diabetes (type 1 or

type 2), the duration of disease, the patient's age at diagnosis, and treatment with insulin<sup>5,8-14</sup>. No studies reported the prevalence of DME with VI. There was a wide range of reported values for prevalence both between and within countries (Figure 1)<sup>5,8-16</sup>.

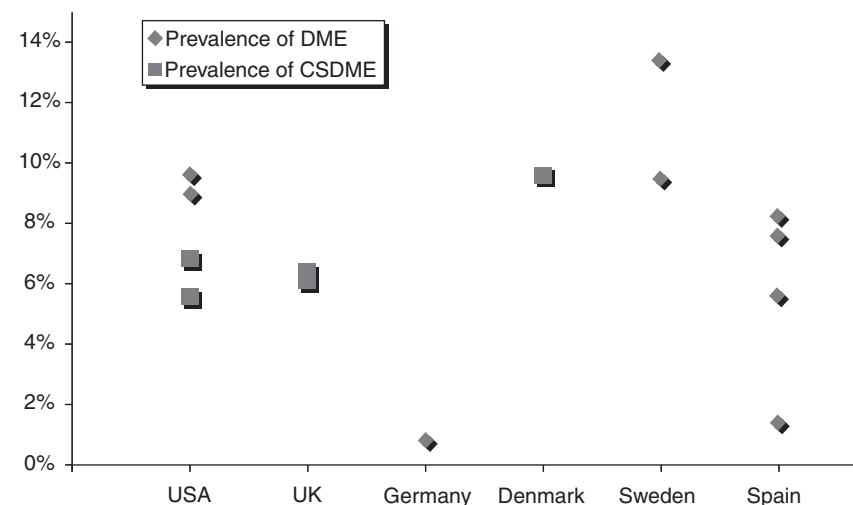
The largest epidemiological study of DME in the US was the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), a prospective, population-based cohort study that enrolled insulin-taking diabetic persons diagnosed before 30 years of age (type 1) and insulin- or non-insulin-taking diabetic persons diagnosed after 30 years of age (type 1 and type 2), living in 11 counties of the state of Wisconsin<sup>5,8</sup>. WESDR showed a direct relationship between the prevalence of DME and the duration since diabetes diagnosis. While the overall prevalence of DME was 11.1% and 8.4% for the younger- (aged ≤30 years) and older- (aged >30 years) onset diabetic patients, respectively, the prevalence was 0% in younger-onset patients with a diagnosis of diabetes for fewer than 5 years and 29% in younger-onset patients with diabetes for 20 years or more. Among older-onset patients, the prevalence varied from 3 to 28% for the corresponding duration of diabetes<sup>5</sup>. In this group, DME was also more prevalent among insulin users than non-insulin users. After 15 years of diabetes duration, DME was present in 20% of those using insulin and 12% not using insulin<sup>5,17</sup>.

In Europe, where the correlation of DME prevalence and duration of disease has not been assessed, the prevalence of DME was shown to be associated with diabetes type and with insulin treatment<sup>9-12</sup>. A longitudinal study of a cohort of 775 diabetic patients participating in the Exeter Diabetic Retinopathy Screening Program in the UK identified that CSDME was present in 6.1% of

diabetes patients at the time of screening (11.5% in type 1 patients, 4.1% in type 2 patients not requiring insulin, and 9.1% in type 2 patients requiring insulin)<sup>12</sup>. Another study, which measured the prevalence of diabetic eye disease in an inner city setting, reported that 6.4% of diabetic patients had CSDME (2.3% in type 1 patients, 5.7% in type 2 patients not requiring insulin treatment, and 16.2% in type 2 patients requiring insulin)<sup>11</sup>. A UK-based epidemiological and economic model projected that DME was expected to be present in 187 842 diabetic patients in 2010, increasing to 235 602 by the year 2020<sup>18</sup>. In Denmark, a study based on the North Jutland County Diabetic Retinopathy Study reported the crude prevalence of CSDME as 9.6% for all diabetic patients; 7.9% for type 1 and 12.8% for type 2 diabetic patients<sup>9,10</sup>.

The prevalence of DME has also been studied in various ethnic groups<sup>15,19-21</sup>. The prevalence of DME and CSDME was shown to be higher in blacks and Hispanics than in Chinese or whites<sup>15</sup> (Figure 2). Other studies also demonstrated the high prevalence in Hispanics<sup>19,20</sup> and blacks<sup>21</sup>. Varma *et al.*, pooled data from three population-based studies (Los Angeles Latino Eye Study, Proyecto VER, Beaver Dam Eye Study). After controlling for traditional risk factors, Hispanics had a higher prevalence of diabetic retinopathy, which might be explained in part by genetic susceptibility<sup>22</sup>.

There were mixed findings regarding whether or not early detection of diabetes and improved disease management resulted in decreased prevalence of DME over time. A systematic literature review and meta-analysis of studies from 1975 to 2008 suggested that the prevalence of DME may be decreasing. Based on 59 studies involving 36 449 untreated patients with diabetic retinopathy, participants



DME: Diabetic macular edema; CSDME: Clinically significant diabetic macular edema

Source: 5;8-16

Figure 1. Prevalence of DME in overall diabetic population, by country.

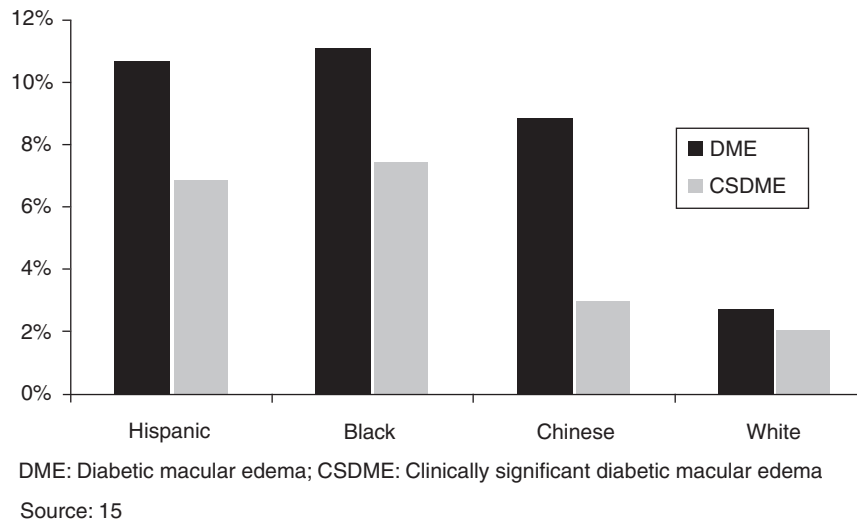


Figure 2. Prevalence rate of DME among various ethnic groups.

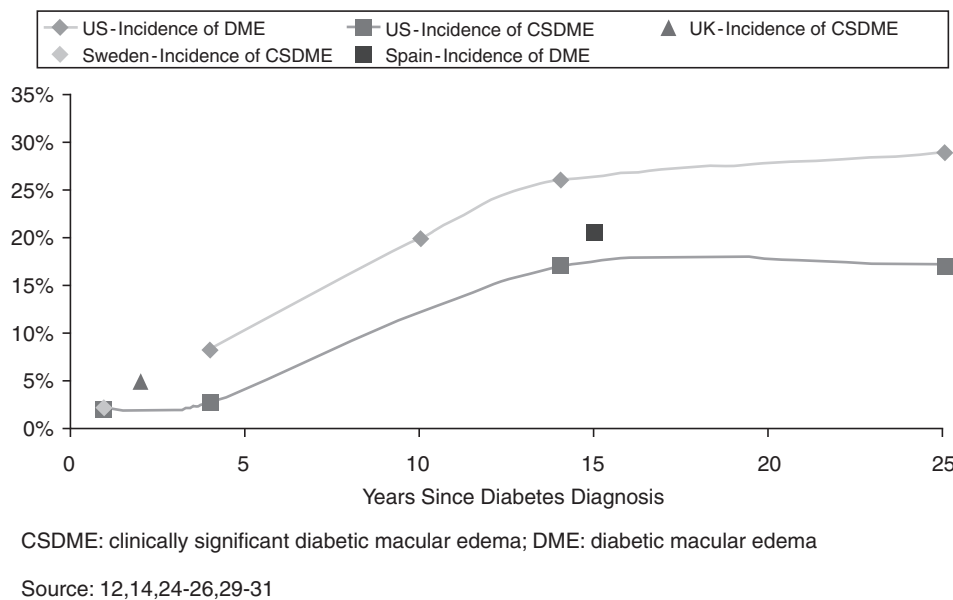


Figure 3. Incidence of DME in overall diabetic population, by country.

in the 1986–2008 period had a lower rate of DME at baseline than those in the 1975–1985 period (10 vs. 30%)<sup>23</sup>. However, a study examining two diabetic populations in 1993 and 2006 in Spain found similar prevalences of DME for type 1 and type 2 diabetic patients during the two time periods<sup>14</sup>.

### Incidence

Incidence can be defined as the number of new cases of a particular disease occurring over a defined period of time in a vulnerable population or presented as the percentage of

cases progressing to the next stage of a disease over a defined period of time. In most publications reviewed, the incidence of DME was reported as a percentage per year or cumulative percentage during a specific period of time. Outside of the US, few studies reported DME incidence. A summary of DME/CSDME incidence by country is provided in Figure 3<sup>12,14,24–26,29–31</sup>.

As with prevalence, incidence of DME was strongly associated with time since diabetes diagnosis. In Sweden, the 1-year incidence of CSDME was 2.3% per year for the overall diabetic population<sup>24</sup>. In the UK, the 2-year incidence of CSDME was 4.79%<sup>12</sup>. In Spain, the 15-year incidence of DME in type 1 diabetic patients was 20.5%<sup>14</sup>.

**Table 1.** Cumulative incidence of DME and CSDME by age and duration of diabetes reported in WESDR.

	Cumulative incidence of DME (%)		Cumulative incidence of CSDME (%)	
	14-year	25-year	14-year	25-year
All groups	26.0	28.6	17.0	16.6
Age (years)				
0–9	10.4	23.2	NR	23.2
10–14	18.7	28.8	NR	19.0
15–19	22.6	26.1	NR	17.7
20–14	26.4	29.7	NR	18.4
25–29	29.3	39.9	NR	21.1
30–34	30.4	29.9	NR	16.5
35+	31.1	23.4	NR	11.0
Diabetes duration (years)				
0–2	12.9	17.7	NR	10.2
3–4	19.3	29.2	NR	14.4
5–9	29.2	34.0	NR	26.4
10–14	33.1	37.7	NR	18.1
15–19	24.1	26.1	NR	12.3
20–24	33.7	36.0	NR	19.5
25–29	27.0	19.1	NR	10.7
30+	16.7	9.6	NR	1.3

CSDME, clinically significant macular edema; DME, diabetic macular edema; NR, not reported.

Source: references 25,26.

The incidence of DME and CSDME by age and duration of diabetes in WESDR is presented in Table 1<sup>25,26</sup>. The 25-year cumulative incidence of DME and CSDME in type 1 diabetic patients was 29% and 17%, respectively, after accounting for the competing risk of death. Although the cumulative risk increased with duration of diabetes, their relationship was not linear, presumably due to the increased competing risk of death with increased age and duration of diabetes<sup>25</sup>. Based on the findings, the authors estimated that over a 25-year period, of the 515 000 to 1.3 million Americans thought to have type 1 diabetes at the time of their study, approximately 149 000–377 000 would develop DME and 88 000–221 000 would develop CSDME<sup>25</sup>.

In addition to duration of the disease, there exists a strong correlation between both the patient's age at onset of diabetes and insulin treatment with the incidence of DME. The 4-year incidence of DME was 8.2% in younger-onset patients using insulin, 8.4% in older-onset patients using insulin, and 2.9% in older-onset patients not treated with insulin<sup>27</sup>. The findings were similar for CSDME, where the 4-year incidence was 4.3% in younger-onset insulin-using patients, 5.1% in older-onset patients requiring insulin, and 1.3% in older-onset patients not requiring insulin<sup>28</sup>. At 10 years, the incidence of DME was 20.1% in the younger-onset patients using insulin, 25.4% in the older-onset patients using insulin, and 13.9% in the older-onset group not using insulin<sup>29</sup>. A Swedish study found a similar pattern, where the 1-year incidence of CSDME was 2.4%, 4.5% and 1.4% in younger-onset patients, older-onset patients using insulin,

and older-onset patients not using insulin, respectively<sup>24</sup>. The incidence of DME was also found to be associated with higher level of glycosylated hemoglobin and more severe retinopathy at the baseline examination<sup>28–30</sup>.

There seems to be a decline in the annualized incidence of DME and CSDME over time. In WESDR, the annualized incidence of DME was found to be lower in the last follow-up period compared with earlier follow-up periods (2.3% from 1980–2 to 1984–6, 2.1% from 1984–6 to 1990–2, 2.3% from 1990–2 to 1994–6, and 0.9% from 1994–6 to 2005–7)<sup>25</sup>. The authors attributed the decline to better glycemic control (i.e., decreasing glycosylated hemoglobin), decreasing mean arterial blood pressure level, and earlier treatment of hypertension. A clinic-based study in Denmark also showed a decline in the incidence of DME in patients over time. The incidence after 15 years of diabetes duration was 11% and 12% for patients diagnosed in 1965–1969 and 1970–1974, respectively, while only 5% for patients diagnosed in 1975–1979<sup>31</sup>.

## Health outcomes

Health outcomes in this review were defined as risk of VI, blindness or death as a result of DME or CSDME.

In the baseline examination in WESDR, 1.4% of the younger-onset diabetic patients had moderate VI (best corrected visual acuity in the better eye of 20/80 to 20/160) and 3.6% were legally blind (visual acuity in the better eye of 20/200 or worse). In the older-onset group, 3.0% had moderate VI and 1.6% were legally blind<sup>32</sup>. The 10-year incidences of blindness were 1.8%, 4.0%, and 4.8% in the younger-onset, older-onset taking insulin, and older-onset not taking insulin groups, respectively<sup>33</sup>. Respective 10-year rates of VI were 9.4%, 37.2%, and 23.9%<sup>33</sup>. The prevalence of VI among younger-onset diabetic patients with a 15- to 19-year duration of diabetes ranged from 2 to 13% (13% among those diagnosed from 1960 through 1969, 2% from 1970 to 1974 and 4% from 1975 to 1979). For those with a 30- to 34-year duration of diabetes, prevalence of VI ranged from 9 to 16%. Patients diagnosed more recently had a lower prevalence of VI, presumably due to the diminishing incidence of proliferative diabetic retinopathy (PDR) and CSDME, possibly resulting from better glycemic control and more timely interventions<sup>34</sup>.

A population-based study of Danish patients with insulin-treated diabetes diagnosed before the age of 30 years found the prevalence of blindness at baseline to be 3.4% for men and 2.6% for women. In the subsequent 8 years of follow-up, the incidence of blindness was 1.0 per 100 person years, which is 50–80 times higher than the rate in the general population<sup>35</sup>. In another Danish study on the epidemiology of blindness in diabetic patients, the prevalence of blindness was 0.6% for type 1 and 1.5% for

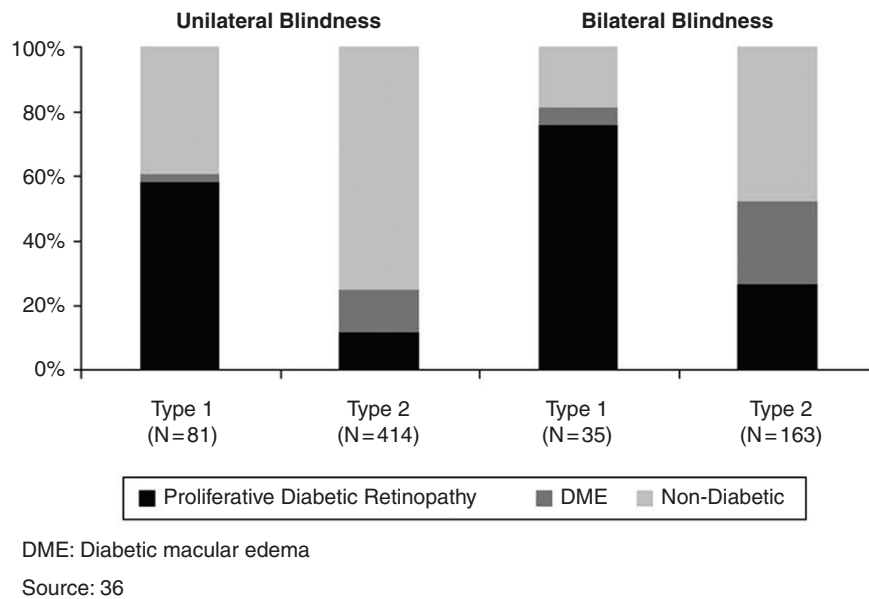


Figure 4. Causes of blindness among diabetic patients.

type 2 diabetic patients. Proliferative diabetic retinopathy (PDR) was the major cause of blindness for type 1 patients, but non-diabetic reasons were the major cause of blindness in the type 2 population (Figure 4). This was presumably due to the fact that type 2 patients usually had a later onset of diabetes, so their vision was more likely to be impacted by complications of aging (e.g., age-related macular degeneration)<sup>36</sup>.

A more recent, population-based cohort study of type 1, insulin-treated diabetic patients in Denmark found the 25-year cumulative crude incidence of blindness to be 7.5%, and the mortality-adjusted incidence of blindness was 9.5%. Presence of DME at baseline was an important risk factor for the development of blindness. Type 1 diabetic patients with DME, in combination with non-proliferative retinopathy and proliferative retinopathy, respectively, had an odds ratio of 6.18 and 8.61 compared to type 1 diabetic patients without DME<sup>37</sup>.

In WESDR, CSDME was associated with increased all-cause and ischemic heart disease mortality in older-onset diabetic patients (HR, 1.55; 95% CI, 1.25–1.92; and HR, 1.56; 95% CI, 1.15–2.13, respectively), when adjusting for age and gender. After controlling for other risk factors, the association remained significant for ischemic heart disease mortality (HR, 1.58; 95% CI, 1.07–2.35;  $p = 0.02$ ) among those taking insulin<sup>8</sup>.

### Treatment patterns, resource use and economic burden

DME is associated with higher rates of resource use compared to diabetic patients without retinal diseases or with other types of diabetic retinopathy<sup>38–40</sup>. Shea *et al.*,

analyzed the administrative claims from a sample of US Medicare beneficiaries from 2000 to 2004. The use of fluorescein angiography, optical coherence tomography (OCT), intravitreal injection, and laser photocoagulation as well as the number of evaluation and management visits were compared between an incident DME cohort and a control cohort of diabetic patients without retinal disease<sup>38</sup>. The study showed that nearly 60% of DME patients received one or more fluorescein angiography in the year after diagnosis; 38% underwent laser photocoagulation; 18% were evaluated with OCT; and 6% received at least one intravitreal injection. Compared with controls, nearly three times as many DME patients visited an ophthalmologist in the year after diagnosis, with an average of 3.9 visits per patient. The same study also showed that treatment patterns for DME changed from 2000 to 2004. In 2000, 43% of the patients with incident DME underwent laser photocoagulation, but by 2004, only 30% of DME patients had this procedure. The decrease in patients treated with laser photocoagulation was concurrent with a shift towards intravitreal injections. In 2000, less than 1% of incident DME patients received an injection, but by 2004, 13% of incident patients had one<sup>38</sup>.

Medicare costs for DME patients were more than 30% higher than for diabetic patients without retinal disease at 1 and 3 years after diagnosis<sup>38</sup>. Inpatient costs constituted almost half of the total costs. Total costs incurred in the year of DME diagnosis were 27% higher than the previous year. After adjustment for age, sex, race/ethnicity, geographic region, and baseline comorbid conditions, DME was a significant independent predictor of total medical costs – associated with 25% higher 1-year costs and 27% higher 3-year costs<sup>38</sup>.

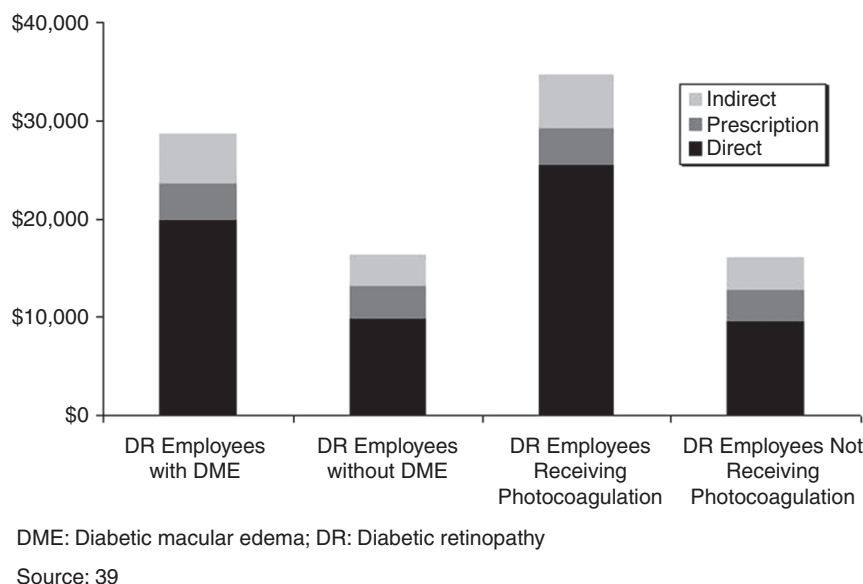


Figure 5. Annual cost of DME and photocoagulation in patients with diabetic retinopathy.

Another retrospective claims analysis of a privately insured population estimated the total direct and indirect costs of DME from an employer perspective<sup>39</sup>. In the study, employees with DME had 75% higher mean annual costs than employees with diabetic retinopathy without DME (US dollars \$28 606 vs. \$16 363,  $p < 0.0001$ ) (Figure 5). This included medical care costs, prescription drug costs, and indirect costs such as employer payments for extended absence from work due to short- or long-term disability and medically-related work-loss days. The higher costs were reflected in hospital inpatient stays (\$7886 vs. \$3551;  $p < 0.0001$ ), emergency department visits (\$247 vs. \$139;  $p < 0.0001$ ), and outpatient department visits (\$10 557 vs. \$5353;  $p < 0.0001$ ). Indirect costs accounted for approximately 20% of total costs among both DME and non-DME employees<sup>39</sup>.

In Germany, DME patients visited an ophthalmologist 7.3 times on average per year. DME patients used almost twice the medical resources as patients with mild or moderate non-proliferative diabetic retinopathy. The cost of DME was estimated to be €3311 from the societal perspective and €2164 from the perspective of the German statutory health insurance. DME was significantly costlier to society than mild and moderate non-proliferative diabetic retinopathy (Figure 6). Medical devices and temporary working disability were the two most costly components. However, the study was based on a very small sample of DME patients ( $n = 46$ )<sup>40</sup>.

Given the profound economic and societal burdens, improving delivery of ophthalmic care to patients with diabetes will be effective both clinically and economically. The American Academy of Ophthalmology suggested that implementation of current screening and treatment

guidelines at the 60% level would yield annual savings of \$101.0 million and 47 374 person-years-sight if all patients received appropriate eye care, the annual savings would be \$167.0 million and 79 236 person-years-sight, one-third of which would arise from treatment of CSDME and two-thirds from treatment of proliferative diabetic retinopathy<sup>41</sup>.

### Humanistic burden

Humanistic burden refers to the impact of a disease on a patient's or caregiver's HRQoL. As a major cause of VI and blindness for both type 1 and type 2 diabetic patients, DME may have a serious impact on patients' HRQoL, which may reduce their ability to manage this disease as well as the underlying diabetes.

In an interview with 701 adult diabetic patients attending clinics in Chicago, researchers measured the utilities for treatments and complications of diabetes. Utilities are used to evaluate subjective preferences for multi-dimensional HRQoL on a scale of 0 to 1, where 0 usually represents the worst possible health, or death, and 1 represents perfect health. Diabetic retinopathy was associated with a utility of 0.53, roughly equivalent to amputation (0.55). Blindness had a mean utility of 0.38, ranking the third lowest among all health states studied following major stroke (0.31) and end-stage renal disease (0.35)<sup>42</sup>. Relative to persons with no VI, persons with moderate-to-severe bilateral or unilateral VI reported greater difficulties in performing vision-dependent daily activities and experienced vision-related dependency and poorer vision-related mental health<sup>43,44</sup>. However, few studies have been performed to explore the relationship between DME and

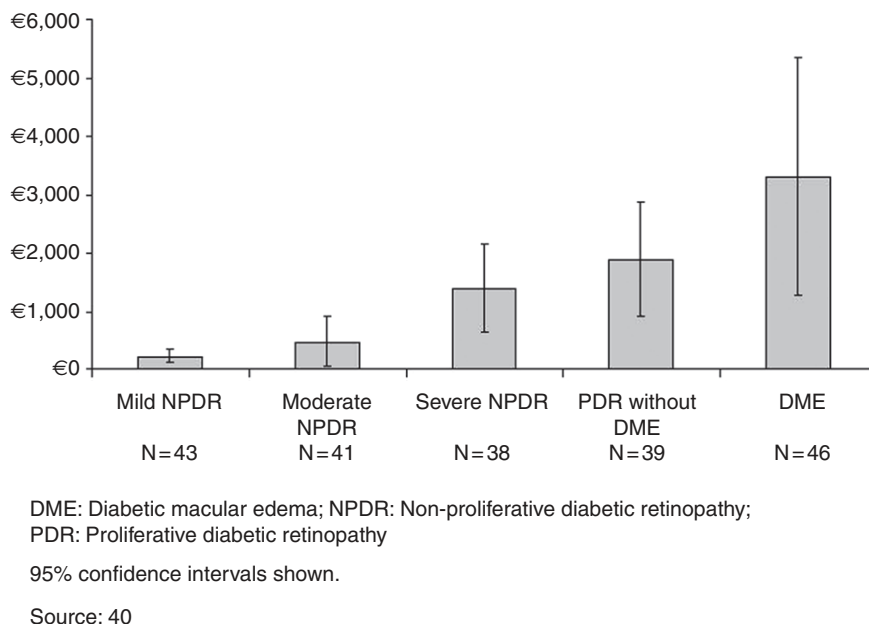


Figure 6. Total costs attributable to diabetic retinopathy from the German societal perspective.

HRQoL. Among a handful of studies performed, DME was shown to have a significant impact on the HRQoL in patients with diabetes<sup>45-47</sup>.

The impact of DME on the HRQoL in 33 patients with type 2 diabetes was examined in a prospective, observational study. Patients with DME scored lower than patients with type 1 diabetes and diabetic retinopathy in terms of general health, quality of vision, and vision-related quality of life (VRQoL) as measured by the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The overall VRQoL for DME patients was lower than patients with cataracts and glaucoma, but comparable to patients with age-related macular degeneration<sup>45</sup>. Another analysis of 207 type 1 and type 2 patients diagnosed with diabetic retinopathy from Germany showed that DME displayed a strong negative effect on visual acuity and on the mental components of a generic questionnaire (SF-12). In addition, the severity of DME was positively associated with binocular vision acuity as well as impaired HRQoL<sup>46</sup>.

Despite the negative impact on patients' perceived functional status and quality of life, studies have shown this impact may attenuate with treatment. A UK study investigated the effects of laser photocoagulation for DME on patients' VRQoL. Among a prospective cohort of 55 patients undergoing laser treatment for DME, eight out of eleven vision-related scores on the NEI VFQ-25 were significantly improved following laser treatment. Improvement on the NEI VFQ-25 composite score was significant in patients younger than 65, in individuals that received more laser burns from photocoagulation treatment, and in those with worse VRQoL at baseline<sup>47</sup>.

## Discussion

Estimation of disease burden may be performed using different approaches. Epidemiological burden characterizes the prevalence and incidence of a disease, which is useful for a government to set research priorities and for policymakers to measure the impact of disease prevention or intervention. Besides prevalence and incidence, burden of illness is also often measured by the economic impact of a disease on a particular nation or healthcare system. If the studies are well-performed, such information can be compared across disease spectrums and highlight the variation of burden across countries.

The majority of the studies identified and reviewed were from the US. Studies on related topics were found from the UK, Germany, Denmark, Finland, Spain, and Sweden. Almost no information was available from Belgium, France, Italy, Norway, Portugal, and The Netherlands. The prevalence and incidence of DME in the US is dominated by studies derived from WESDR, the largest epidemiological study with the longest follow-up. Since patients were followed up for 25 years, WESDR provided excellent information on the incidence of DME and CSDME over time. However, WESDR was initiated from 1980 to 1982; therefore, the disease progression and treatment may not reflect the current environment. More recent studies are based on smaller patient populations and are often limited in scope. Some of these studies were clinic-based as opposed to population-based; thus, the representativeness of the results may be questionable. In Europe, most identified studies have relatively small patient populations, usually with a limited scope.

Therefore, compared to the US, the reported prevalence and incidence of DME and CSDME ranged more widely. The values are sometimes conflicting due to the heterogeneous nature of studies (e.g., patient selection, diabetes type) and the disparity between study methods (e.g., DME screening and diagnosis). Direct comparison of these study findings is not appropriate, which highlights the need for consistent data capture within and between European countries.

Incidence of DME and CSDME appears to be declining, as shown by WESDR<sup>25</sup>. Data suggest that this decrease may be attributed to a reduction of hyperglycemia and hypertension<sup>25,29</sup>. Since the inception of WESDR is relatively old, whether early detection of diabetes or recent advances in medical therapies to control hyperglycemia and hypertension have lessened the incidence of DME or CSDME cannot be concluded. However, given the rising prevalence of diabetes worldwide, it is expected that the number of patients affected by DME will increase dramatically.

In a cost-conscious environment, evaluating the economic impact of a disease or disease intervention is becoming increasingly important and is often second to clinical value in determining access to treatment for patients. This is particularly relevant in Europe, where single payer markets determine the majority of coverage (i.e., access). As healthcare costs continue to rise, more emphasis is being placed on understanding the economic implications of disease progression and its treatment. However, as this review reveals, very little economic information regarding DME and its treatments exists, highlighting an urgent need to bridge this gap given the rise in the global prevalence of diabetes.

The comprehensiveness of an economic study depends on the benefit design and coverage of a health insurance plan. For example, both direct non-medical costs – such as caregiver expenses, home healthcare expenses, and lost wages to patients and caregivers – and indirect costs (productivity costs) usually are not covered by an insurance plan. While only direct medical costs are captured, other costs are not, thereby preventing a full societal perspective on the total burden of disease. None of the economic studies reviewed included all of the relevant cost components associated with an illness (e.g., direct medical, direct non-medical, and indirect costs). Most studies only reported direct medical costs. Only one study included both direct medical cost and indirect costs in the US<sup>39</sup>. Since DME affects diabetic patients of all ages, indirect costs should be given particular attention in future studies because of the potential importance of productivity loss due to VI and blindness resulting from DME. Despite the limitations of these studies, DME is consistently shown to be associated with higher resource use and costs compared to other diabetic retinopathies,

and substantially higher than diabetic patients without retinal diseases<sup>38–40</sup>.

In addition, the available economic studies from the US are primarily based on analyses of administrative claims data. Issues around the use of administrative databases include accurately identifying the disease and comprehensively capturing all relevant cost components. As administrative claims list the International Classification of Diseases (ICD) codes in order to be paid, the validity of patient identification and cost classification depends upon the extent to which the disease and the use of healthcare resources are accurately coded. The only European economic study included in this review assessed costs through questionnaires and medical chart abstraction, however, the sample size is very small (46 DME patients)<sup>40</sup>.

The impact of DME on patients' HRQoL is almost entirely lacking from the literature. Limited evidence suggests that DME decreases both vision and health-related quality of life; however, laser photocoagulation may improve HRQoL. With many novel treatments being introduced for the management of DME, measuring HRQoL will likely play an important role in the decision to offer treatment and in monitoring relevant health gains that may be derived from new interventions.

## Conclusion

There is limited knowledge of the DME epidemiology in the European patient populations. Across all countries assessed, very little economic information concerning DME is available. Existing studies, however, do suggest that medical expenditures for DME patients are much higher than for diabetic patients without retinal diseases, representing a substantial economic and societal burden. Based on the scarcity of data, coordinated efforts for consistent data capture in Europe and more recent population-based prospective studies in the US are needed to fully understand the epidemiology, treatment patterns, and economic and humanistic burden of DME.

## Transparency

### Declaration of funding

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### Declaration of financial/other relationships

E.C., M.L. and M.L. have disclosed that they are employees of Quorum Consulting Inc. M.L. D.L., E.C., and K.V. have also disclosed that they are consultants for, and have received funding for this research from, Novartis. M.G. has disclosed that she is an employee of Novartis Pharma AG. K.V. has disclosed that she is

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## References

- American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2008. Available at: <http://www.aao.org/ppp> [Last accessed 2 February 2010]
- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998; 21:1414-31
- Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27: 1047-53
- Diabetes Statistics. American Diabetes Association. Available at: <http://www.diabetes.org/diabetes-statistics.jsp> 2009. [Last accessed 2 February 2010]
- Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology* 1984; 91:1464-74
- Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology* 1991;98: 741-56
- Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye* 2004;18:963-83
- Hirai FE, Knudtson MD, Klein BE, et al. Clinically significant macular edema and survival in type 1 and type 2 diabetes. *Am J Ophthalmol* 2008;145:700-6
- Knudsen LL, Lervang HH, Lundbye-Christensen S, et al. The North Jutland County Diabetic Retinopathy Study: population characteristics. *Br J Ophthalmol* 2006;90:1404-9
- Knudsen LL, Lervang HH, Lundbye-Christensen S, et al. The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema. *Br J Ophthalmol* 2007; 91:1593-5
- Broadbent DM, Scott JA, Vora JP, et al. Prevalence of diabetic eye disease in an inner city population: the Liverpool Diabetic Eye Study. *Eye* 1999; 13:160-5
- Ling R, Ramsewak V, Taylor D, et al. Longitudinal study of a cohort of people with diabetes screened by the Exeter Diabetic Retinopathy Screening Programme. *Eye* 2002;16:140-5
- Reuterving CO, Kratholm J, Wachtmeister L. Ophthalmic health care in diabetes mellitus: a cross-sectional study in northern Sweden. *Ophthalmic Epidemiol* 1999;6:267-78
- Romero-Aroca P, Fernandez-Alart J, Baget-Bernaldiz M, et al. Diabetic retinopathy epidemiology in type 2 diabetic patients. Effect of the changes in the diagnostic criteria and stricter control of the diabetes between 1993 and 2005 on the incidence of diabetic retinopathy. *Arch Soc Esp Oftalmol* 2007;82:209-18
- Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol* 2006;141:446-55
- Blum M, Kloos C, Muller N, et al. Prevalence of diabetic retinopathy. Check-up program of a public health insurance company in Germany 2002-2004. *Ophthalmologie* 2007;104:499-500, 502-4
- Klein R, Davis MD, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. A comparison of retinopathy in younger and older onset diabetic persons. *Adv Exp Med Biol* 1985;189:321-35
- Future sight loss in the decade 2010 to 2020: an epidemiological and economic model. Report prepared for RNIB by Darwin Minassian and Angela Reidy. July 2009. EpiVision. Available at: <http://www.vision2020uk.org.uk/ukvisionstrategy/page.asp?section=74> [Last accessed 2 March 2010]
- West SK, Klein R, Rodriguez J, et al. Diabetes and diabetic retinopathy in a Mexican-American population: Proyecto VER. *Diabetes Care* 2001;24: 1204-9
- Varma R, Torres M, Pena F, et al. Prevalence of diabetic retinopathy in adult Latinos: the Los Angeles Latino eye study. *Ophthalmology* 2004;111:1298-1306
- Roy MS, Klein R. Macular edema and retinal hard exudates in African Americans with type 1 diabetes: the New Jersey 725. *Arch Ophthalmol* 2001;119:251-9
- Varma R, Klein R, West SK, et al. Are Latinos at greater risk for diabetic retinopathy than whites? Pooled findings from 3 population-based studies. *Invest Ophthalmol Vis Sci* 2005;46:1164
- Flynn HW, Wong T, Mwamburi M, et al. Progression to proliferative diabetic retinopathy and severe visual impairment: a systematic review and meta-analysis [abstract]. Association for Research in Vision and Ophthalmology (ARVO) 2009 Annual Meeting. May 3-7, Fort Lauderdale, FL
- Henricsson M, Sellman A, Tyrberg M, et al. Progression to proliferative retinopathy and macular oedema requiring treatment. Assessment of the alternative classification of the Wisconsin Study. *Acta Ophthalmol Scand* 1999;77:218-22
- Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology* 2009;116: 497-503
- Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;105:1801-15
- Klein R, Moss SE, Klein BE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. XI. The incidence of macular edema. *Ophthalmology* 1989;96:1501-10
- Klein R, Klein BE, Moss SE. The Wisconsin epidemiologic study of diabetic retinopathy: an update. *Aust N Z J Ophthalmol* 1990;18:19-22
- Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology* 1995;102:7-16
- Klein R, Klein BE, Moss SE. How many steps of progression of diabetic retinopathy are meaningful? The Wisconsin epidemiologic study of diabetic retinopathy. *Arch Ophthalmol* 2001;119:547-553
- Rossing K, Jacobsen P, Rossing P, et al. Improved visual function in IDDM patients with unchanged cumulative incidence of sight-threatening diabetic retinopathy. *Diabetes Care* 1998;21:2007-15
- Klein R, Klein BE, Moss SE. Visual impairment in diabetes. *Ophthalmology* 1984;91:1-9
- Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. *Ophthalmology* 1994;101:1061-70
- Klein R, Lee KE, Knudtson MD, et al. Changes in visual impairment prevalence by period of diagnosis of diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology* 2009;116:1937-42
- Sjolie AK, Green A. Blindness in insulin-treated diabetic patients with age at onset less than 30 years. *J Chronic Dis* 1987;40:215-20
- Jeppesen P, Bek T. The occurrence and causes of registered blindness in diabetes patients in Arhus County, Denmark. *Acta Ophthalmol Scand* 2004; 82:526-30

37. Grauslund J, Green A, Sjolie AK. Blindness in a 25-year follow-up of a population-based cohort of Danish type 1 diabetic patients. *Ophthalmology* 2009;116:2170-4
38. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol* 2008; 126:1748-54
39. Lee LJ, Yu AP, Cahill KE, et al. Direct and indirect costs among employees with diabetic retinopathy in the United States. *Curr Med Res Opin* 2008; 24:1549-59
40. Happich M, Reitberger U, Breitscheidel L, et al. The economic burden of diabetic retinopathy in Germany in 2002. *Graefes Arch Clin Exp Ophthalmol* 2008;246:151-9
41. Javitt JC, Aiello LP, Bassi LJ, et al. Detecting and treating retinopathy in patients with type 1 diabetes mellitus. Savings associated with improved implementation of current guidelines. *American Academy of Ophthalmology. Ophthalmology* 1991;98:1565-73
42. Huang ES, Brown SE, Ewigman BG, et al. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care* 2007; 30:2478-83
43. Lee DJ, Gomez-Marin O, Lam BL, et al. Visual impairment and morbidity in community-residing adults: the national health interview survey 1986-1996. *Ophthalmic Epidemiol* 2005;12:13-17
44. Varma R, Wu J, Chong K, et al. Impact of severity and bilaterality of visual impairment on health-related quality of life. *Ophthalmology* 2006; 113:1846-53
45. Hariprasad SM, Mieler WF, Grassi M, et al. Vision-related quality of life in patients with diabetic macular oedema. *Br J Ophthalmol* 2008;92:89-92
46. Davidov E, Breitscheidel L, Clouth J, et al. Diabetic retinopathy and health-related quality of life. *Graefes Arch Clin Exp Ophthalmol* 2009;247:267-72
47. Tranos PG, Topouzis F, Stangos NT, et al. Effect of laser photocoagulation treatment for diabetic macular oedema on patient's vision-related quality of life. *Curr Eye Res* 2004;29:41-9