Risk of glaucoma after vitreoretinal surgery – Findings from a population-based cohort study

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ABSTRACT.

Purpose: To investigate the association between different types of vitrectomy and risk of different types of glaucoma and to determine the effect of systemic medication and diabetes status on this risk.

Methods: A population-based nested case–control study included individuals of age ≥ 18 years who had undergone single vitrectomy, vitrectomy with retinal procedure, or combined phaco-vitrectomy between 2001 and 2010. End of follow-up was 2017. Odds ratio (OR) for the development of glaucoma after different types of vitrectomy and 95% confidence interval (CI) were based on conditional logistic regression models. For every glaucoma case, five controls were matched by age, sex, start of follow-up year, and hospital district.

Results: The cohort (n = 37 687), of which 52.8% was female, consisted of 6552 individuals diagnosed with glaucoma and 31 135 controls matched by age, sex, and hospital district. Vitrectomy was performed on 103 eyes in the glaucoma group and 158 eyes in the control group. As regards the risk of any glaucoma, the risk was lowest in eyes that underwent combined phaco-vitrectomy (OR: 2.7, 95% CI: 1.8–4.1), followed by single vitrectomy (OR: 3.15, 95% CI: 2.1–4.8), and highest in eyes that underwent vitrectomy with retinal procedure (OR: 4.5, 95% CI: 2.7–7.4). Diabetes had no effect (OR: 0.96, 95% CI: 0.92–1.01), but 5-year systemic statin use slightly decreased glaucoma risk (OR: 0.86, 95% CI: 0.77–0.97).

Conclusions: Vitreoretinal surgery was associated with an increased glaucoma risk; the risk being related to the complexity of vitrectomy. Long-term systemic statin therapy may decrease glaucoma risk, while diabetes had no association.

Key words: epidemiology – glaucoma – population-based study – vitrectomy

Introduction

Glaucoma is the leading cause of irreversible blindness globally. The risk and subtypes of glaucoma vary in different populations. Currently, the number of people aged 40–80 years with glaucoma worldwide is 64.3 million but expected to increase to more than 110 million by 2040 (Tham et al. 2014).

Primary open-angle glaucoma (POAG) is characterized by degeneration of retinal ganglion cells often associated with an increase in intraocular pressure (IOP) due to hindered aqueous humour drainage through the trabecular meshwork (TM) and uveoscleral pathway. Recent studies have highlighted the role of low-grade inflammation, oxidative stress and damage to the TM in the development of OAG (Weinreb et al. 2014; Siegfried & Shui 2019). On the other hand, the aetiology of secondary glaucoma (SG) is more complex, including inflammation, lens- and drug-induced responses, retinal vascular diseases, certain syndromes, tumours, trauma, and/or anterior and posterior segment surgery. In recent years, the epidemiology of glaucoma subtypes has changed, showing increase in drug-induced, anterior segment surgery-related and syndrome-associated SG cases (Gong et al. 2021).

Vitreoretinal surgery has advanced extensively during the last decades, being currently the third most performed eye surgery after cataract and refractive surgery (El-Amir et al. 2009; Wubben et al. 2016). Some vitreoretinal surgery manoeuvres, such as stripping of the internal limiting membrane (ILM), can lead to adverse events including Müller cell dysfunction, eccentric paracentral macular holes,
macular microscotomata, and retinal dimpling (Díaz-Valverde & Wu 2018). The perioperative use of dyes, retinal photoagulation, cryotherapy, intravitreal anti-VEGF, use of fluid-air exchange/perfluorocarbon/gas/silicone oil (SO) and other treatments may have an impact on long-term visual outcomes and development of glaucoma after vitreoretinal surgery.

Today, the precise pathogenesis of glaucoma after vitreoretinal surgery remains unknown. In addition, the treatment of glaucoma after vitreoretinal surgery may be challenging due to noncompliance to conventional therapies (Koreen et al. 2012). Furthermore, systemic diseases such as diabetes per se or systemic medication may play a role in the individual risk of post-vitreoretinal glaucoma (Feldman-Billard & Dupas 2021).

Generally, it has been reported that there is an increased risk of OAG after pars plana vitrectomy (Chang 2006; Mansukhani et al. 2018; Miele et al. 2018). However, findings related to association of glaucoma with vitreoretinal surgery have been heterogenous, suggesting that further studies need to be conducted in more homogenous cohorts (Miele et al. 2018). Currently, there is a strong need to investigate the association of less complication prone macular surgery (vitrectomy) and more complication prone complex vitreoretinal surgery (vitrectomy with retinal procedure) with the risk of glaucoma. Also, evaluating the risk of glaucoma after combined phaco/lensectomy-vitrectomies is warranted.

The main objective of this longitudinal population-based study was to investigate the association between different types of vitreoretinal surgery and risk of glaucoma. We examined the risk of OAG or other type of glaucoma in eyes that underwent three types of vitreoretinal surgery based on the complexity of posterior segment pathology.

Methods

Study design was longitudinal historic population-based. The original FIN-CARING2 study population included 398 708 individuals. Of them, 199 354 subjects had diabetes, and an equivalent reference population was non-diabetic, and matched by age, sex and region, as described (Niskanen et al. 2020). Subjects with diabetes had insulin or oral antidiabetic prescriptions and medication reimbursement claims.

Inclusion criteria

Out of 244 100 individuals selected for the study of glaucoma incidence, we constructed a nested case–control study population aiming to sample five controls (n = 31 135) for each glaucoma case (n = 6552), matched by age (within 1 year), sex, start of follow-up calendar year (within 1 year), and hospital district. In the analysis, some cases had less than five controls. The start of follow-up was from January 1, 2001, to December 31, 2010, and the end of follow-up was December 31, 2017, covering a 17-year study period. Individuals with a start date before January 1st 2001 were excluded in order to secure a 5-year history of hospital or tertiary health care records for the whole study population before the start of follow-up. Individuals with already diagnosed glaucoma or who had undergone vitreoretinal surgery before start of follow-up were excluded.

Glaucoma types in the cohort

Glaucoma was classified using diagnostic International Classification of Diseases (ICD)-10 code H40.1 for open angle glaucoma (OAG), consisting of five subtypes: exfoliation glaucoma (H40.10), normal tension glaucoma (H40.11), pigmentary glaucoma (H40.12), chronic primary open-angle glaucoma (H40.13), and unspecified open-angle glaucoma (H40.19) (in the Finnish system they are: https://koodistopalvelu.kanta.fi/codeserver/pages/classification-view-page.xhtml?classificationKey = 23&versionKey = 58).

The other glaucoma cases included unspecified glaucoma (H40.2–8) or glaucoma secondary to other eye disorders. First, we analysed individuals who were diagnosed with any glaucoma (a). Next we subgrouped glaucoma cases to (b) OAG or (c) other type of glaucoma taking into account the exact type of vitreoretinal eye surgery.

Performed vitreoretinal surgical procedures

The primary vitreoretinal surgical procedures were recorded as follows (http://urn.fi/URN:ISBN:978-952–245-858-2): vitrectomy through pars plana (PPV) (CKD91; Vit); combined PPV and retinal procedure (CKD92; VitRet); combined phacoemulsification and/or lensectomy with or without intraocular lens (IOL) implantation together with PPV (CKD94; PhacoVit). The main indications for vitreoretinal surgery according to ICD-10 codes were as follows: (a) rhegmatogenous retinal detachment (RRD, H33.0); (b) vitreoretinal interface diseases (macular hole (MH) or macular pucker; H35.37/H35.38; (c) diabetic retinopathy (DR) (diabetic maculopathy and proliferative DR H36.01, H36.03); (d) vitreous haemorrhage (H43.1) (Loukovaara et al. 2018). Typically, CKD91 vitrectomy was performed on eyes with least severe posterior segment pathology such as vitreoretinal interface diseases, or vitreous haemorrhage. Eyes with more complex conditions such as RRD or DR underwent CKD92 surgery (including removal of membranes, use of perfluorocarbon if needed, endolaser, fluid-air exchange, with air, gas (SF6, C2F6, C3F8) or SO endotamponade). CKD94 vitrectomy included cataract extraction, IOL implantation and macular surgery. CKD94 procedure covered also complicated cataract surgery in need of vitrectomy, removal of lens remnants with or without IOL implantation.

We aimed to identify the exact ICD-10 diagnoses of vitreoretinal surgeries and evaluate the risk of glaucoma within each of the three groups (i.e. CKD91, CKD92, and CKD94). Since 38 out of 261 surgeries (14.5%) missed accurate ICD-10 diagnosis, this additional data could not be analysed reliably.

Exclusion criteria

Individuals who underwent a combined procedure on vitreous body and retina including encircling seleral buckle/explant or band (CKD93) were excluded due to complex retinal pathology and vitreoretinal surgery. Encircling band per se has the potential to compress episcleral veins and cause IOP elevation.

Systemic medication and comorbidities

Data on medication prescriptions and reimbursements were obtained from
the Social Insurance Institute, which provides national public health insurance to all residents in Finland (Kela 16/522/2012). We identified systemic medications at baseline by dispensed prescriptions and comorbidities by granted special medication reimbursements. Systemic medications included angiotensin agents, calcium channel antagonists, beta-blockers, diuretics, metformin, statins, selective serotonin reuptake-inhibitors (SSRI), tricyclic antidepressants and drugs for Alzheimer’s disease. Information of the following systemic diseases were collected: thyroid insufficiency, adenocortical insufficiency, severe psychotic and other severe mental disorders, cancer, chronic cardiac insufficiency, chronic hypertension, chronic coronary heart disease, and chronic arrhythmias. Altogether, the following baseline variables were available: age, sex, diabetes (yes/no), socioeconomic group, other systemic comorbidities, systemic medication, and hospital district.

Main objective
The main objective was to study the risk of new onset OAG or other type of glaucoma after vitreoretinal surgery. Special interest was paid to the exact type of vitreoretinal surgery (CKD91, CKD92, CKD94), as well as diabetes status and exposure to statin therapy before and at the time of surgery.

Ethical considerations
We obtained the approval from the Ethics Committee of Faculty of Medicine, University of Helsinki, 17 January 2012 (Ref: 02/2012). Approvals to extend the original study plan and research group were granted by register holders (the Social Insurance Institute (Kela 29/522/2019), and the Institution for Health and Welfare (THL/486/5.05.00/2019 and THL/3157/14.02.00/2020)).

Statistical analysis
We modelled the risk of glaucoma after vitreoretinal surgery using a conditional logistic regression model that takes matching into account. Odds ratio (OR) and 95% confidence interval (CI) are reported. All analyses were carried out separately for the two glaucoma endpoints (OAG and other glaucoma).

Operated eyes were divided into three groups according to the vitrectomy procedure received: Vit (CKD91, single vitrectomy), VitRet (CKD92, combined vitrectomy with retinal procedure), and PhacoVit (CKD94, combined phaco-vitrectomy). The analysis comparing the association of statin use was conducted using vitrectomy subgroups. Calculations were carried out with R language (R Core Team 2019).

Results
Of the study population (n = 37 687), 52.8% were female (n = 19 895) (Table 1). Patients were operated in 21 districts in Finland. A quarter of the population was from the capital region, Helsinki and Uusimaa district (n = 9639; 25.6%). Out of all glaucoma cases, 33.8% (n = 2216) were diagnosed as OAG and 66.2% (n = 4336) were of other glaucoma types.

The most common systemic comorbidity was chronic hypertension (n = 10 708; 28.4%). The three most used systemic medications were metformin (n = 10 370, 27.5%), beta-blockers (n = 9529, 25.3%), and statins (n = 7830, 20.8%). Compared to matched controls, glaucoma cases had less frequently severe systemic comorbidities at baseline such as psychotic and other severe mental disorders (p = 0.010), chronic coronary heart disease (p < 0.001), and Alzheimer’s disease (p = 0.006). In addition, glaucoma cases used less often beta-blockers (p < 0.001), diuretics (p = 0.002), metformin (p = 0.001), or statins at the time of vitreoretinal surgery (p < 0.001).

Association of vitreoretinal surgical procedure with the risk of glaucoma
During our study, 261 individuals, consisting of 103 glaucoma cases and 158 age- and sex-matched controls underwent one of three types of vitreoretinal surgeries: CKD91 vitrectomy (Vit, n = 99), CKD92 vitrectomy with retinal procedure (VitRet, n = 63), and CKD94 phaco-vitrectomy (PhacoVit, n = 99).

Based on the conditional logistic regression model, the risk of any glaucoma (OAG or other glaucoma type) was increased after all three types of vitreoretinal surgeries, but there were clear differences between the vitreoretinal surgery groups (Table 2). The risk of any glaucoma was lowest in the eyes that underwent combined phaco-vitrectomy (PhacoVit; OR: 2.7, 95% CI: 1.8–4.1), followed by single vitrectomy (Vit; OR: 3.15, 95% CI: 2.1–4.8), being highest in the eyes that underwent vitrectomy with retinal procedure (VitRet; OR: 4.5, 95% CI: 2.7–7.4).

According to the glaucoma subtype analysis, the risk of OAG was increased after single vitrectomy (Vit; OR: 2.33, 95% CI: 1.21–4.50), and vitrectomy with retinal procedure (VitRet; OR: 3.66, 95% CI: 1.54–8.70). However, risk of OAG was not affected in eyes that underwent combined phaco-vitrectomy (PhacoVit; OR: 1.42, 95% CI: 0.70–2.89). The risk of other glaucoma was higher than the risk of OAG in all three vitrectomy subgroups: (PhacoVit; OR: 4.58, 95% CI: 2.62–8.00; Vit; OR: 5.37, 95% CI: 2.88–9.99; and VitRet; OR: 4.06, 95% CI: 2.39–6.91). Adjusted risks were in accordance with non-adjusted.

Diabetes was not associated with the risk of any type of glaucoma after vitreoretinal surgery (adjusted OR: 0.94, 95% CI: 0.87–1.03) and did not show any association in the glaucoma subgroup analyses either (not shown). When socioeconomic status was taken into account, the risk of glaucoma after vitreoretinal surgery was not increased in any socioeconomic group compared to upper-level employees (Table 2). Of note, the risk was lower in self-employed, manual workers and pensioners.

Next, we included time since surgery as an additional predictor in the conditional logistic regression models as follows: no surgery, less than 1 year, 1–2 years, 2–5 years, over 5 years. However, we did not find any association between time since surgery and risk of glaucoma in our study (data not shown).

Exposure to statin therapy before surgery
Since statins have been suggested to reduce the risk of glaucoma (McCann et al. 2016), we found it reasonable to study whether lipid-lowering statin therapy modulates the risk profile of glaucoma after vitreoretinal surgery. Statin therapy was the third most common systemic medication within the cohort. Of the 7830 statin users, 6487 (20.8%) belonged to age- and sex-
matched controls and 1343 were glaucoma cases (20.5%; \( p = 0.552 \)). Cumulative exposure to statin therapy slightly decreased the risk of any glaucoma (OR: 0.86, 95% CI: 0.77–0.97) (Table 3). However, exposure time shorter than 5 years was not associated with the risk of any glaucoma. According to the glaucoma subtype analysis, both 4-year exposure (OR: 0.87, 95% CI: 0.78–0.97) and 5-year exposure (OR: 0.81, 95% CI: 0.69–0.95) to statin therapy before vitreoretinal surgery slightly decreased the risk of the other glaucoma, but no difference was found in the OAG cases (not shown). Shorter duration of statin therapy (less than 3 years) had no association with the risk of either OAG or other glaucoma after vitreoretinal surgery.

### Discussion

#### Main finding

In this nested case–control study, we analysed 261 individuals who had undergone one of three main types of vitreoretinal surgical procedures in Finland during years 2001–2010, and of whom 103 developed glaucoma and 158 were age, sex and hospital district matched controls. The risk of any glaucoma was increased after all three types of vitreotomy, confirming recent findings (Mansukhani et al. 2018; Miele et al. 2018). Of note, the risk of any glaucoma was highest among the eyes that underwent vitreotomy with retinal procedure (VitRet group) and lowest in the eyes that underwent combined cataract surgery and vitreotomy (PhacoVit group).

#### Results in context with the published literature

Vitreoretinal surgery has advanced extensively during the last decades, and combined cataract and vitreotomy procedures are commonly performed in Europe. The risk of any glaucoma being lowest in the group that underwent combined cataract and vitreotomy may be related to a tendency of IOP to decrease after cataract surgery (Mansberger et al. 2012; Masis Solano & Lin 2018). In addition, the eyes that undergo combined phaco-vitreotomy are often those with vitreoretinal interface diseases undergoing routine macular surgery. Previous studies have also shown that in eyes receiving macular surgery for disorders such as epiretinal fibrosis and/or macular hole, the condition is less inflammatory, but more neurodegenerative (Öhman et al. 2018).

In our sub-analysis, patients undergoing combined phaco-vitreotomy had more...

### Table 1. Basic characteristics of study population at baseline.

|                      | Controls (n) (%) | Glaucoma cases (n) (%) | Overall (n) (%) |
|----------------------|-----------------|------------------------|-----------------|
| Study population     | 31 135          | 6552                   | 37 687          |
| Sex                  |                 |                        |                 |
| Female               | 16 428 (52.8)   | 3467 (52.9)            | 19 895 (52.8)   |
| Start of follow-up   |                 |                        |                 |
| 2001                 | 3449 (11.1)     | 742 (11.3)             | 4191 (11.1)     |
| 2002                 | 3201 (10.3)     | 687 (10.5)             | 3888 (10.3)     |
| 2003                 | 3055 (9.8)      | 650 (9.9)              | 3705 (9.8)      |
| 2004                 | 3391 (10.9)     | 718 (11.0)             | 4109 (10.9)     |
| 2005                 | 2764 (8.9)      | 584 (8.9)              | 3348 (8.9)      |
| 2006                 | 2586 (8.3)      | 552 (8.4)              | 3138 (8.3)      |
| 2007                 | 3336 (10.7)     | 689 (10.5)             | 4025 (10.7)     |
| 2008                 | 3885 (12.5)     | 803 (12.3)             | 4688 (12.4)     |
| 2009                 | 3044 (9.8)      | 625 (9.5)              | 3669 (9.7)      |
| 2010                 | 2424 (7.8)      | 732 (42.0)             | 2926 (7.8)      |
| Type of glaucoma     |                 |                        |                 |
| No glaucoma          | 30 529 (98.1)   | 0 (0)                  | 30 529 (81.0)   |
| OAG                  | 261 (0.8)       | 2216 (33.8)            | 2477 (6.6)      |
| Other glaucoma       | 345 (1.1)       | 4336 (66.2)            | 4681 (12.4)     |
| Socioeconomic status |                 |                        |                 |
| Upper-level employee | 1795 (5.8)      | 442 (6.7)              | 2237 (5.9)      |
| Self-employed        | 1508 (4.8)      | 263 (4.0)              | 1771 (4.7)      |
| Lower-level employee | 2857 (9.2)      | 635 (9.7)              | 3492 (9.3)      |
| Student              | 106 (0.3)       | 22 (0.3)               | 128 (0.3)       |
| Retiree              | 19 649 (63.1)   | 4144 (63.2)            | 23 793 (63.1)   |
| Other                | 2127 (6.8)      | 427 (6.5)              | 2554 (6.8)      |
| Diabetes             |                 |                        |                 |
| Yes (n, %)           | 15 055 (48.4)   | 3100 (47.3)            | 18 155 (48.2)   |
| Comorbidities (n, %) |                 |                        |                 |
| Hypertension         | 8923 (28.7)     | 1785 (27.2)            | 10 708 (28.4)   |
| CHD                  | 3420 (11.0)     | 618 (9.4)              | 4038 (10.7)     |
| Thyroid insufficiency| 1069 (3.4)      | 215 (3.3)              | 1284 (3.4)      |
| Cancer               | 1044 (3.4)      | 217 (3.3)              | 1261 (3.3)      |
| Mental disease       | 964 (3.1)       | 163 (2.5)              | 1127 (3.0)      |
| Chronic arrhythmias  | 723 (2.3)       | 158 (2.4)              | 881 (2.3)       |
| Cardiac insufficiency| 722 (2.3)       | 134 (2.0)              | 856 (2.3)       |
| Systemic medication  |                 |                        |                 |
| Metformin            | 8677 (27.9)     | 1693 (25.8)            | 10 370 (27.5)   |
| \( \beta \)-blockers | 8050 (25.9)     | 1479 (22.6)            | 9529 (25.3)     |
| Statin               | 6487 (20.8)     | 1343 (20.5)            | 7830 (20.8)     |
| Angiotensin agonist  | 4828 (15.5)     | 1044 (15.9)            | 5872 (15.6)     |
| Ca-antagonist        | 3839 (12.3)     | 754 (11.5)             | 4593 (12.2)     |
| Diuretics            | 3526 (11.3)     | 653 (10.0)             | 4179 (11.1)     |
| SSRI                 | 998 (3.2)       | 174 (2.7)              | 1172 (3.1)      |
| Alzheimer therapy    | 157 (0.5)       | 16 (0.2)               | 173 (0.5)       |
| Memantine            | 42 (0.1)        | 3 (0.0)                | 45 (0.1)        |
| Time since surgery (years) |       |                       |                 |
| (0,1]                | 3 (0.0)         | 2 (0.0)                | 5 (0.0)         |
| (1,2]                | 6 (0.0)         | 1 (0.0)                | 7 (0.0)         |
| (2,5]                | 42 (0.1)        | 25 (0.4)               | 67 (0.2)        |
| (5, Inf)             | 107 (0.3)       | 75 (1.1)               | 182 (0.5)       |
| No surgery           | 30 977 (99.5)   | 6449 (98.4)            | 37 426 (99.3)   |

**Abbreviations:** CHD = coronary heart disease; POAG = primary open angle glaucoma; SSRI = selective serotonin reuptake-inhibitors; Vitrectomy through pars plana (CKD91; Vit); Combined vitrectomy and retinal procedure (CKD92; VitRet); Combined phacoemulsification-lensectomy with or without intraocular lens (IOL) implantation together with vitrectomy through pars plana (CKD94; PhacoVit).

Time since surgery was used as predictor. As a reference group we used cases where under 1 year had passed since surgery.
Any glaucoma

| Type of surgery | Controls, n | Glaucoma, n | OR (95% CI) | Adjusted OR (95% CI) |
|----------------|-------------|-------------|-------------|----------------------|
| No surgery     | 30,977      | 6449        | (reference) | (reference)          |
| Vit (CKD91)    | 61          | 38          | 3.15 (2.09–4.75) | 3.17 (2.10–4.78) |
| VitRet (CKD92) | 33          | 30          | 4.49 (2.74–7.36) | 4.39 (2.67–7.20) |
| PhacoVit (CKD94)| 64       | 35          | 2.70 (1.78–4.08) | 2.68 (1.77–4.06) |

OAG

| Type of surgery | Controls, n | Glaucoma, n | OR (95% CI) | Adjusted OR (95% CI) |
|----------------|-------------|-------------|-------------|----------------------|
| No surgery     | 20,456      | 4265        | (reference) | (reference)          |
| Vit (CKD91)    | 33          | 25          | 2.33 (1.21–4.50) | 2.31 (1.19–4.46) |
| VitRet (CKD92) | 19          | 21          | 3.21 (1.39–7.43) | 3.14 (1.35–7.28) |
| PhacoVit (CKD94)| 30       | 25          | 1.42 (0.70–2.89) | 1.37 (0.67–2.79) |

“Other glaucoma”

| Type of surgery | Controls, n | Glaucoma, n | OR (95% CI) | Adjusted OR (95% CI) |
|----------------|-------------|-------------|-------------|----------------------|
| No surgery     | 10,521      | 2184        | (reference) | (reference)          |
| Vit (CKD91)    | 28          | 13          | 3.90 (2.28–6.66) | 3.92 (2.30–6.70) |
| VitRet (CKD92) | 14          | 9           | 5.40 (2.90–10.05) | 5.28 (2.83–9.84) |
| PhacoVit (CKD94)| 34       | 10          | 4.14 (2.44–7.05) | 4.20 (2.47–7.14) |

Diabetes

| Type of surgery | Controls, n | Glaucoma, n | OR (95% CI) | Adjusted OR (95% CI) |
|----------------|-------------|-------------|-------------|----------------------|
| No             | 16,080      | 3452        | (reference) | (reference)          |
| Yes            | 15,055      | 3100        | 0.96 (0.92–1.01) | 0.94 (0.87–1.03) |

Socioeconomic status

| Type of surgery | Controls, n | Glaucoma, n | OR (95% CI) | Adjusted OR (95% CI) |
|----------------|-------------|-------------|-------------|----------------------|
| Upper-level employees | 1795 | 442 | 1.00 (1.00–1.00) | (reference) |
| Self-employed       | 1508       | 263         | 0.70 (0.59–0.83) | 0.71 (0.60–0.84) |
| Lower-level employee | 2857      | 635         | 0.91 (0.79–1.04) | 0.91 (0.79–1.04) |
| Manual worker       | 3093       | 619         | 0.81 (0.71–0.93) | 0.82 (0.71–0.94) |
| Student             | 106        | 22          | 0.82 (0.51–1.32) | 0.84 (0.52–1.35) |
| Pensioner           | 19,649     | 4144        | 0.78 (0.68–0.89) | 0.79 (0.69–0.90) |
| Other               | 2127       | 427         | 0.80 (0.69–0.93) | 0.81 (0.69–0.94) |

Risk of glaucoma after three types of vitreoretinal surgery (CKD91, CKD92, CKD94) are presented in all eyes, and both subgroups i.e. open angle glaucoma (OAG) and other glaucoma. Odds ratio (OR) and 95% confidence interval (CI) are based on conditional logistic regression model, adjustment with diabetes and socio-economic group. Vitrectomy through pars plana (CKD91; Vit); combined vitrectomy and retinal procedure (CKD92; VitRet); and combined phacoemulsification and intraocular lens (IOL) implantation together with vitrectomy through pars plana (CKD94; PhacoVit).

The subgroup other glaucoma covers unspecified glaucoma and glaucoma secondary to other eye disorders.

† Only matching by sex, age, calendar year, and region taken into account.
‡ All types of glaucoma combined.

Noteworthy, the complement cascade, the toll-like receptors, and tumour necrosis factor (TNF-α) pathway have been implicated in the pathogenesis of glaucoma, DR and RRD (Tezel 2008; Luo et al. 2010; Texel et al. 2010; Loukovaara et al. 2015; Damnak et al. 2021; Ohman et al. 2021). Taken together, the increased risk of glaucoma may be explained by oxidative stress, neuroinflammation, proteolytic degradation, degenerative changes, dysregulation of ocular hemodynamics, genetic factors, as well as aberrant cellular signalling known to be implicated in neurodegeneration and cell loss associated with both central nervous system and retinal disorders (Tezel 2008; Inyushin et al. 2019; Rodriguez Villanueva et al. 2020; Ohman et al. 2021).

Other less studied pathological mechanisms likely to be involved in the optic neuropathy or secondary glaucoma after vitreoretinal surgery could be related to newly discovered lymphatic system (Wostyn et al. 2015; Wostyn 2021). Post-vitreectomy, the rapid changes of IOP and composition of the vitreous substitute (whether gas or SO) as well as changes in cerebrospinal fluid surrounding the optic nerve could have impact on the pathogenesis of glaucoma. Decades ago, it was shown that fluids from the vitreous body and the optic nerve move from opposite directions and converge at the optic nerve head (Hayreh 1978).

Thus, it is possible that vascular and lymphatic circulatory dysfunction may play a role in the pathogenesis of glaucomatous damage in vitrectomized eyes. The more complex the vitreoretinal surgery, the more breakdown of inner and outer blood-retinal barrier there is in the posterior segment (Coca-Prados 2014). In addition, the more complex the posterior segment pathology, the more pro-inflammatory and pro-fibrotic cytokines and growth factors will be released both before surgery and during tissue manipulation at the time of surgery (Pastor et al. 2016; Ohman et al. 2021). As expected, in our sub-analysis, the risk of glaucoma was highest in the group that underwent vitrectomy combined with retinal procedure, the risk being 3.2-fold for OAG and 5.4-fold for other type of glaucoma. Herein, in addition to simple membrane peeling, intraoperative surgical manoeuvres and tissue manipulation such as use of...
Diabetes was not associated with the risk of glaucoma after endorectomy. Diabetic patients may have shallower anterior chambers and thicker crystalline lenses than non-diabetic patients (Kocatürk et al. 2014). Numerous studies have, however, shown that cataract surgery improves aqueous humour dynamics by lowering the IOP in both diabetic and non-diabetic eyes (Mansberger et al. 2012; Masis Solano & Lin 2018; Bayat & Akpolat 2021).

In this study, cumulative exposure to statin treatment longer than 4 years was associated with a slightly decreased risk of other type of glaucoma after vitreoretinal surgery, though no such association was found for OAG. This finding is of interest, since decreased risk of glaucoma could be related to pleiotropic effects of statins before surgery and their ability to modulate surgery-related post-operative inflammation (Tuuminen et al. 2015). Of note, Stein et al. (2012) showed that statin use could protect against both incident glaucoma and need for glaucoma medication, suggesting that the benefit of statin use might play out early during glaucoma development. Based on our findings, we can only speculate that statins might prevent inflammation and/or fibrosis of the anterior segment in the regions of conventional aqueous outflow (in TM and Schlemm’s canal) (Ferrer 2006). Statins may also make the retinal tissues less vulnerable to operation-related damage during vitrectomy, if used long-term before vitreoretinal surgery. Glaucoma can also result from obstruction of drainage structures in the anterior segment (in TM) due to post-vitrectomy complications such as rebleeding, the risk of which is highest among eyes that have undergone complex vitreotomies. Rebleeding can trigger rise in IOP, inflammation and fibrosis. Thus, systemic medication such as statins, administered long-term prior to surgery as well as during post-operative management, could be the key to success when evaluating the risk of glaucoma and other adverse effects such as reoperations and PVR formation after vitreoretinal surgery (Loukovaara et al. 2018). However, more exact associations of systemic statin therapy and development of glaucoma could not be investigated in our observational setting, since the number of patients undergoing vitreoretinal surgery was low.

The nested case-control design that was utilized in our current study is known to give good estimates for hazard rates that are approximated by odds ratios (Biesheuvel et al. 2008). However, like in all observational studies, it is not guaranteed that all pertinent risk factors are available to be used in statistical modelling. Therefore, it is possible that there is remaining confounding or other types of bias affecting the study results.

**Conclusions**

Our population-based study investigated the association of glaucoma with vitreoretinal surgery in Finland. Although real-world evidence may be subject to bias and confounding...
factors, and despite the limitations of our study, we could show that the risk of any glaucoma is increased after most performed vitreoretinal surgical procedures. Interestingly, diabetes was not associated with the risk of glaucoma after vitreoretinal surgery. In addition, although exposure to statin in the long-term preoperative period was associated with reduced glaucoma risk after vitreoretinal surgery, no strong conclusions can be drawn from the sub-analysis without information on the dose or type of statin. Further prospective research is thus warranted to elucidate the risk and clinical course of glaucoma after vitreoretinal surgery and in relation to novel anti-inflammatory and anti-fibrosis agents.

Authorship
All authors have given their final approval of the version to be published; and SL and JH have given the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SL, JH. Acquisition, analysis, or interpretation of data: JH, AK, AM, KM, GW, CP. Critical revision of the manuscript: JH, SL, AK, MM, CD, AB, SG. Writing the article: JH, AK, AM, KM, GW, CP. Final approval of the version to be published: SL, JH.

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