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Androgen deprivation therapy and the risk of diabetes in men with prostate cancer

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Androgen deprivation therapy and the risk of diabetes in men with prostate cancer

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Abstract

Objectives: To examine the risk of type 2 diabetes in prostate cancer patients and its association with androgen deprivation therapy.

Design and participants: Patients diagnosed with prostate cancer in the Lithuanian male population between January 1, 2003 and December 31, 2012 were identified through the Lithuanian Cancer registry. All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database to obtain information regarding the diagnosis of diabetes mellitus and information on prescriptions of antiandrogens and gonadotropin-releasing hormone (GnRH) agonists. Prostate cancer patients were followed up until the diagnosis of type 2 diabetes, or December 31, 2017, or date of death, whichever came first. Cox proportional hazard models were used to estimate the risk of type 2 diabetes in prostate cancer patients with or without ADT exposure.

Results: 27 580 men were diagnosed with prostate cancer, out of whom 14 502 (52.58%) did not receive ADT and 13 078 (47.42%) were treated with ADT. The incidence of type 2 diabetes for all prostate cancer patients was 7.4/1000 person-years, for men on GnRH agonists 9.0/1000 person-years and 5.8/1000 person-years for men on antiandrogens. There was an increased risk of developing type 2 diabetes comparing androgen deprivation therapy users and non-users (HR = 1.49, 95% CI = 1.34 to 1.66).

Conclusion: This study showed an increased risk of diabetes in prostate cancer patients treated with ADT in comparison to ADT-free patient cohort. GnRH agonist users showed higher susceptibility, while the group on antiandrogen monotherapy showed no such increase.

Strengths and limitations

- Large cohort size, population-based design and long observation time (up to 15 years) are strengths of our study.
- Lack of clinical information regarding treatment modality, applied for patients in combination with ADT, especially information on surgical castration.
- Differences in ADT treatment groups could be influenced by selection bias, as GnRH agonists are used for treatment of metastatic disease, however differences in ADT treatment groups remains after adjusting to stage of disease.

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Competing interests

The authors declare no conflict of interest.

Abbreviations:

AA – antiandrogens

ADT – androgen deprivation therapy

CI – confidence interval

GnRH - gonadotropin-releasing hormone

HR - Hazard ratio

NHIF - National Health Insurance Fund

SE – standard error

1. Introduction

Prostate cancer is one of the most prevalent malignancies and the second leading cause of cancer-related deaths in men worldwide [1]. The growth of prostate cancer cells is dependent on androgens; therefore, androgen deprivation therapy (ADT) is recommended treatment in men with metastatic prostate cancer. ADT is also used in clinically locally advanced prostate cancer in conjunction with radiotherapy as either adjuvant or neoadjuvant therapy [2].

ADT results in a rapid decrease in serum concentrations of testosterone to castration level by reducing testicular androgens secretion or by inhibiting the androgen receptors. Androgen deprivation can also be achieved with surgery (orchiectomy) or medications (gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists or oral antiandrogens (AA)). In addition, complete androgen blockade using combination of GnRH analogues and antiandrogens can also be used in some clinical cases [3]. If prostate cancer patients progress to castrate resistance state, it is recommended to continue ADT [4].

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3 Hypogonadism produced by ADT leads to adverse effects, such as increased risk of
4 cardiovascular disease and metabolic syndrome, anaemia, sexual dysfunction, decreased
5 genital size, gynaecomastia, diminished quality of life, cognitive lesion, hot flushes and
6 reduced bone mineral density [5–8]. One of the newest long-term effect observed in other
7 studies is ADT increasing insulin resistance and having an impact on type 2 diabetes
8 development [5,9–12].
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11 In our large population-based cohort study, we examined the risk of type 2 diabetes in
12 prostate cancer patients and its association with ADT.
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14 **2. Research Design and Methods**

15 **Study population**

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17 Patients diagnosed with prostate cancer in the entire Lithuanian male population between
18 January 1, 2003 and December 31, 2012 were identified through the Lithuanian Cancer
19 registry. The database includes information about the date of diagnosis, age at diagnosis,
20 tumour stage (classified by TNM), cause and date of death. Lithuanian data on cancer
21 incidence is included Cancer Incidence in Five Continents, a longstanding collaboration
22 between the International Agency for Research on Cancer and the International Association
23 of Cancer Registries, which serves as a unique source of cancer incidence data from high-
24 quality population-based cancer registries around the world [13].
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27 All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database
28 in order to obtain information regarding the diagnosis of diabetes mellitus and information on
29 prescriptions of antiandrogens and GnRH agonists. The National Health Insurance Fund
30 (NHIF) database contains demographic data and entries on the primary and secondary
31 healthcare services provided, emergency and hospital admissions and prescriptions of
32 reimbursed medications. Data from the Lithuanian NHIF database encompasses about 98%
33 of inpatient cases and 90% of outpatient visits (up to 100% of primary health care visits) in
34 Lithuania, covering the entire territory of the country [14].
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37 In total between January 1, 2003 and December 31, 2012 29247 cases of prostate cancer were
38 identified. Prostate cancer patients with date of prostate cancer diagnosis equal to the date of
39 death (607 cases) and patient with diabetes mellitus diagnosis before prostate cancer
40 diagnosis (1060 cases), were excluded from the analysis. 27580 prostate cancer patients
41 were included in this study.
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Statistical analysis

We analyzed risk of diabetes between men on ADT, and prostate cancer patients not treated with ADT. Identified patients were followed till the date of type 2 diabetes diagnosis, or December 31, 2017, or date of death, whichever came first.

In order to evaluate incidence of diabetes caused by ADT we calculated exact person-years at risk for each patient.

Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence intervals to compare risk of diabetes in groups of prostate cancer patients by ADT exposure. Multivariate adjusted Cox proportional hazards models including age and stage at diagnosis were conducted to estimate the effect of ADT on diabetes risk. Association between duration of GnRH agonists use and diabetes risk was assessed by dividing duration into the following intervals: 0-1, 1-2, 2-3, 3-5 and more than 5 years.

All statistical analyses were carried out using STATA statistical software (version 15.1; College Station, TX, USA). The Vilnius Regional Biomedical Research Ethics Committee approved this study.

Patient and public involvement

This article does not contain any studies with human participants. No patients were involved in this study. Our study was based on retrospective data collected in national health insurance fund database.

3. Results

Table 1 presents baseline characteristics of 27 580 men who were diagnosed with prostate cancer, out of whom 14 502 (52.58%) did not receive ADT and 13 078 (47.42%) were treated with ADT. The vast majority of patients (92.25%) received GnRH agonists and 7.75% received antiandrogens.

During follow-up period there were 1371 prostate cancer patients diagnosed with type 2 diabetes. The incidence of type 2 diabetes for all prostate cancer patients (ADT users and ADT non-users) was 7.4/1000 person-years. For those who have never used ADT the incidence was 6.0/1000 person-years. Type 2 diabetes Incidence for ADT users was 8.8/1000 person-years, for men on GnRH agonists 9.0/1000 person-years and 5.8/1000 person-years for men on antiandrogens (**Table 2**).

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3 There was a significantly increased risk of developing of type 2 diabetes comparing ADT
4 users with ADT non-users (HR = 1.49, 95% CI = 1.34 to 1.66) (**Table 3**). Adjusted hazards
5 models for patient's age and tumour's stage also showed a statistically higher risk of
6 developing type 2 diabetes (aHR = 1.47, 95% CI = 1.32 to 1.64) in ADT users group. As
7 compared to ADT non-users the usage of GnRH agonists was associated with an increased
8 risk of type 2 diabetes (HR = 1.53, 95% CI = 1.38 to 1.71), however, there was no significant
9 association between oral antiandrogen monotherapy and outcome.

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12 **Table 4** reports diabetes risk in the group of GnRH agonists users. There were no significant
13 differences in risk by duration of GnRH agonists exposure duration.

20 21 **4. Discussion**

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23 Our prostate cancer patient cohort study showed increased risk of diabetes in ADT users
24 compared to ADT-free patient cohort. In accordance with other studies, elevated risk was
25 found among GnRH agonist users, while in the antiandrogen monotherapy group no such
26 increase was observed.

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30 ADT, which decreases serum testosterone levels by inhibiting testosterone production, has
31 been the first line treatment for men with locally advanced or metastatic prostate cancer since
32 1940 [15]. ADT can reduce circulating testosterone levels to castration levels, however,
33 previous studies have shown that low levels of testosterone might decrease lean body mass
34 growth and increase fat deposition, also might cause insulin resistance by reducing insulin
35 sensitivity [16,17]. The association between ADT users in prostate cancer patients and insulin
36 resistance was identified in *Basaria et al.* study. Patients who received ADT for at least 12
37 months had an increased risk of developing insulin resistance and hyperglycaemia. Forty-four
38 percents of ADT patients had glucose levels in the diabetic range and the duration of ADT
39 was linked to the severity of these metabolic abnormalities [9]. *Bosco et al.* meta-analysis
40 results suggested that ADT usage for prostate cancer patients increased risk of diabetes by
41 36% [18]. In our study we also observed that ADT usage increases the risk of diabetes
42 compared to ADT non-users (HR: 1.49 95% CI 1.34 to 1.66).

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53 *Keating et al.* found that the treatment with GnRH agonists is associated with an increased
54 risk of type 2 diabetes compared to ADT non-users (HR for GnRH agonists versus no ADT:
55 1.44, 95% CI: 1.34 – 1.55) [5]. *Crawley et al.* evaluated the risk of type 2 diabetes for the
56 patients treated with GnRH agonists or antiandrogens. They found that GnRH agonists
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3 increase the risk of type 2 diabetes. In contrast management with antiandrogens was not
4 associated with type 2 diabetes [12]. In our study we showed the highest risk of diabetes was
5 in GnRH agonists users group (HR: 1.53, 95% CI 1.38 to 1.71). This data is in line with
6 above mentioned studies.
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11 The duration of ADT is a very important factor when trying to establish the link between type
12 2 diabetes and ADT. *Keating et al.* showed increase risk of type 2 diabetes for patients on
13 GnRH agonists, however, this study had a relatively short duration (up to 25 months) [5]. To
14 our knowledge *Crawley et colleagues* were the first that evaluated different types of ADT and
15 the effect of treatment duration. They examined the risk of type 2 diabetes with up to ten
16 years of exposure. In their study they revealed that patients on GnRH agonists during the first
17 3 years (2 – 2.5 years of exposure HR: 1.68, 95% CI 1.40 to 2.02) had the highest risk of
18 developing type 2 diabetes [12]. Similarly, we showed that the highest incidence of diabetes
19 was in the 3-year-exposure group (HR: 1.77, 95% CI 1.44 to 2.18), however, the risk was
20 also significantly elevated in other categories.
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29 Intermittent ADT treatment was suggested as alternative treatment to continuous ADT with
30 possibly fewer complications and better quality of life [19]. *Rezaei et al.* study's results
31 showed that in short-term treatment with intermittent ADT there was no difference in fasting
32 blood glucose, which suggests lower risks of diabetes mellitus in this group of patients [20].
33 Thus, difference in diabetes risk increase between non-users and ADT users could be
34 mitigated by the proportion of intermittent ADT user in our cohort, whom we could not
35 identify from our database. However, according to general used prostate cancer treatment
36 guidelines intermittent ADT could be applicable only for very small and well-informed
37 fraction of prostate cancer patients [21]. Therefore, we consider that this should not influence
38 the final results of our study.
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46 Large cohort size, population-based design and long observation time (up to 15 years) are
47 strengths of our study. Main limitation of our study is lack of clinical information regarding
48 treatment modality, applied for patients in combination with ADT, especially information on
49 surgical castration. This type of ADT is not common in clinical practice, therefore inclusion
50 of those cases in non-ADT patients group has no substantial effect on diabetes risk
51 evaluation. Another limitation is that differences in ADT treatment groups could be
52 influenced by selection bias, as GnRH agonists are used for treatment of metastatic disease,
53 however differences in ADT treatment groups remains after adjusting to stage of disease.
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5. Conclusion

This study showed that there is increased risk of diabetes in prostate cancer patients treated with ADT in comparison with ADT-free patient cohort. GnRH agonist users showed higher susceptibility while the group on antiandrogen monotherapy showed no such increase.

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Table 1 Baseline characteristics of men with prostate cancer by ADT use.

	All Patients	ADT Free Cohort	ADT users	AA	GnRH
n (%)	27580 (100%)	14502 (52.58%)	13078 (47.42%)	1014 (7.75%)	12064 (92.25%)
Mean follow up time, years (SE)	6.74 (3.64)	6.54 (3.56)	6.97 (3.73)	7.12 (4.34)	6.95 (3.68)
Age					
Mean age at diagnosis, years (SE)	67.81 (8.61)	68.71 (10.05)	66.81 (6.53)	66.10 (6.50)	66.87 (6.53)
<65	9327 (33.82%)	5120 (35.31%)	4207 (32.17%)	374 (36.88%)	3833 (31.77%)
65-74	12441 (45.11%)	4715 (32.51%)	7726 (59.08%)	580 (57.20%)	7146 (59.23%)
>75	5812 (21.07%)	4667 (32.18%)	1145 (8.76%)	60 (5.92%)	1085 (9.00%)
Stage					
I	1913 (6.94%)	1380 (9.52%)	533 (4.08%)	25 (2.47%)	508 (4.21%)
II	11986 (43.46%)	6660 (45.92%)	5326 (40.72%)	460 (45.36%)	4866 (40.34%)
III	7157 (25.95%)	2671 (18.42%)	4486 (34.30%)	214 (21.10%)	4272 (35.41%)
IV	1461 (5.06%)	663 (4.57%)	798 (6.10%)	105 (10.36%)	693 (5.74%)
Unknown	5063 (18.36%)	3128 (21.57%)	1935 (14.80%)	210 (20.71%)	1725 (14.30%)

Table 2 Incidence of type 2 diabetes per 1000 person-years in prostate cancer patients by ADT use

	Number of patients	Number of events	Incidence rate
All patients	27580	1371	7.4
ADT non-users	14502	570	6.0
ADT users	13078	801	8.8
GnRH agonists users	12064	759	9.0
Antiandrogen users	1014	42	5.8

Table 3 Hazard ratios (HR) for type 2 diabetes in prostate cancer by use of ADT.

	HR	95% CI	aHR*	95% CI
ADT free cohort	ref.	-	ref.	
ADT users	1.49	1.34 to 1.66	1.47	1.32 to 1.64
GnRH agonists users	1.53	1.38 to 1.71	1.51	1.35 to 1.69
Antiandrogen users	1.02	0.75 to 1.40	1.02	0.74 to 1.39

Table 4 Hazard ratios (HR) for type 2 diabetes in men with prostate cancer on GnRH agonists for different periods of exposure.

Years of exposure	Number of events	Number of patients	HR	95% CI	aHR*	95% CI
0–1	369	6800	1.41	1.23 to 1.61	1.38	1.21 to 1.58
1–2	139	2177	1.60	1.33 to 1.93	1.59	1.32 to 1.92
2–3	105	1330	1.77	1.44 to 2.18	1.76	1.42 to 2.17
3–5	96	1151	1.74	1.40 to 2.16	1.73	1.42 to 2.17
>5	50	606	1.58	1.18 to 2.11	1.57	1.17 to 2.10

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42 Abstract

43 **Objectives:** To examine the risk of type 2 diabetes in prostate cancer patients and its
44 association with androgen deprivation therapy.

45 **Design and participants:** We performed a retrospective cohort study of patients diagnosed
46 with prostate cancer in the Lithuanian male population between January 1, 2003 and December
47 31, 2012 who were identified through the Lithuanian Cancer registry. All prostate cancer cases
48 were linked to the National Health Insurance Fund (NHIF) database to obtain information
49 regarding the diagnosis of diabetes mellitus and information on prescriptions of antiandrogens
50 and gonadotropin-releasing hormone (GnRH) agonists. Prostate cancer patients were followed
51 up until the diagnosis of type 2 diabetes, or December 31, 2017, or date of death, whichever
52 came first. Cox proportional hazard models were used to estimate the risk of type 2 diabetes in
53 prostate cancer patients with or without ADT exposure.

54 **Results:** 27 580 men were diagnosed with prostate cancer, out of whom 14 502 (52.6%) did
55 not receive ADT and 13 078 (47.4%) were treated with ADT. The incidence of type 2 diabetes
56 for all prostate cancer patients was 7.4/1000 person-years, for men on GnRH agonists 9.0/1000
57 person-years and 5.8/1000 person-years for men on antiandrogens. There was an increased risk
58 of developing type 2 diabetes comparing androgen deprivation therapy users and non-users
59 (HR = 1.49, 95% CI = 1.34 to 1.66).

60 **Conclusion:** This study showed an increased risk of diabetes in prostate cancer patients treated
61 with ADT in comparison to ADT-free patient cohort. GnRH agonist users showed higher
62 susceptibility, while the group on antiandrogen monotherapy showed no such increase.

63 Strengths and limitations

- 64 • Large cohort size, population-based design and long observation time (up to 15 years)
65 are strengths of our study.
- 66 • Lack of clinical information regarding treatment modality, applied for patients in
67 combination with ADT, especially information on surgical castration.
- 68 • Differences in ADT treatment groups could be influenced by selection bias, as GnRH
69 agonists are used for treatment of metastatic disease, however differences in ADT
70 treatment groups remains after adjusting to stage of disease.

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3 **72 Abbreviations:**
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5 **73 AA** – antiandrogens
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7 **74 ADT** – androgen deprivation therapy
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9 **75 CI** – confidence interval
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11 **76 GnRH** - gonadotropin-releasing hormone
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13 **77 HR** - Hazard ratio
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15 **78 NHIF** - National Health Insurance Fund
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17 **79 SE** – standard error
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25 **81 1. Introduction**

26 **82** Prostate cancer is one of the most prevalent malignancies and the second leading cause of
27 **83** cancer-related deaths in men worldwide [1]. The growth of prostate cancer cells is dependent
28 **84** on androgens; therefore, androgen deprivation therapy (ADT) is recommended treatment in
29 **85** men with metastatic prostate cancer. ADT is also used in clinically locally advanced prostate
30 **86** cancer in conjunction with radiotherapy as either adjuvant or neoadjuvant therapy [2].
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35 **87** ADT results in a rapid decrease in serum concentrations of testosterone to castration level by
36 **88** reducing testicular androgens secretion or by inhibiting the androgen receptors. Androgen
37 **89** deprivation can also be achieved with surgery (orchiectomy) or medications (gonadotropin-
38 **90** releasing hormone (GnRH) agonists, GnRH antagonists or oral antiandrogens (AA)). In
39 **91** addition, complete androgen blockade using combination of GnRH analogues and
40 **92** antiandrogens can also be used in some clinical cases [3]. If prostate cancer patients progress
41 **93** to castrate resistance state, it is recommended to continue ADT [4].
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48 **94** Hypogonadism produced by ADT leads to adverse effects, such as increased risk of
49 **95** cardiovascular disease and metabolic syndrome, anaemia, sexual dysfunction, decreased
50 **96** genital size, gynaecomastia, diminished quality of life, cognitive lesion, hot flushes and
51 **97** reduced bone mineral density [5–8]. One of the newest long-term effect observed in other
52 **98** studies is ADT increasing insulin resistance and having an impact on type 2 diabetes
53 **99** development [5,9–12].
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3 100 In our large population-based cohort study, we examined the risk of type 2 diabetes in prostate
4 cancer patients and its association with ADT.
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6 7 102 **2. Research Design and Methods**

8 9 103 **Study population**

10 104 We performed a retrospective cohort study of patients diagnosed with prostate cancer in the
11
12 105 entire Lithuanian male population between January 1, 2003 and December 31, 2012 who were
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14 106 identified through the Lithuanian Cancer registry. The database includes information about the
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16 107 date of diagnosis, age at diagnosis, tumour stage (classified by TNM), cause and date of death.
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18 108 Lithuanian data on cancer incidence is included Cancer Incidence in Five Continents, a
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20 109 longstanding collaboration between the International Agency for Research on Cancer and the
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22 110 International Association of Cancer Registries, which serves as a unique source of cancer
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24 111 incidence data from high-quality population-based cancer registries around the world [13].
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27 112 All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database
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29 113 in order to obtain information regarding the diagnosis of diabetes mellitus and information on
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31 114 prescriptions of antiandrogens and GnRH agonists. Data linkage between databases was based
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33 115 on the personal identification code, which is unique to each resident in Lithuania. The National
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35 116 Health Insurance Fund (NHIF) database contains demographic data and entries on the primary
36
37 117 and secondary healthcare services provided, emergency and hospital admissions and
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39 118 prescriptions of reimbursed medications. Data from the Lithuanian NHIF database
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41 119 encompasses about 98% of inpatient cases and 90% of outpatient visits (up to 100% of primary
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43 120 health care visits) in Lithuania, covering the entire territory of the country [14]. Male patients,
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45 121 who in NHIF database were registered with type 2 diabetes (International Classification of
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47 122 Diseases (ICD)-10 code E11) were considered diabetic. Men who received GnRH agonists or
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49 123 antiandrogens for at least six months were defined as ADT users.

50 124 In total between January 1, 2003 and December 31, 2012 29247 cases of prostate cancer were
51
52 125 identified. Prostate cancer patients with date of prostate cancer diagnosis equal to the date of
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54 126 death (607 cases) and patient with diabetes mellitus diagnosis before prostate cancer diagnosis
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56 127 (1060 cases), were excluded from the analysis. 27580 prostate cancer patients were included
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58 128 in this study.

59 129 **Statistical analysis**

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3 130 We analyzed risk of diabetes between men on ADT, and prostate cancer patients not treated
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5 131 with ADT. Identified patients were followed till the date of type 2 diabetes diagnosis, or
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7 132 December 31, 2017, or date of death, whichever came first.

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9 133 In order to evaluate risk of developing diabetes among ADT users in prostate cancer patients'
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11 134 cohort we calculated exact person-years at risk for each patient.

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13 135 Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence
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15 136 intervals to compare risk of diabetes in groups of prostate cancer patients by ADT exposure.
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17 137 Multivariate adjusted Cox proportional hazards models including age and stage at diagnosis
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19 138 were conducted to estimate the effect of ADT on diabetes risk. Association between duration
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21 139 of GnRH agonists use and diabetes risk was assessed by dividing duration into the following
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23 140 intervals: 0-1, 1-2, 2-3, 3-5 and more than 5 years. GnRH agonists' users to the duration group
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25 141 were assigned by cumulative exposure.

26 142 All statistical analyses were carried out using STATA statistical software (version 15.1;
27
28 143 College Station, TX, USA). The Vilnius Regional Biomedical Research Ethics Committee
29
30 144 approved this study.

31 145 **Patient and public involment**

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34 146 This article does not contain any studies with human participants. No patients were involved
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36 147 in this study. Our study was based on retrospective data collected in national health insurance
37
38 148 fund database.

39 40 149 **3. Results**

41
42 150 **Table 1** presents baseline characteristics of 27 580 men who were diagnosed with prostate
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44 151 cancer, out of whom 14 502 (52.6%) did not receive ADT and 13 078 (47.4%) were treated
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46 152 with ADT. The vast majority of patients (92.2%) received GnRH agonists and 7.8% received
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48 153 antiandrogens. There were significant differences between ADT free cohort and ADT users
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50 154 according the mean age and stage distribution.

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52 155 During follow-up period there were 1371 prostate cancer patients diagnosed with type 2
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54 156 diabetes. The incidence of type 2 diabetes for all prostate cancer patients (ADT users and ADT
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56 157 non-users) was 7.4/1000 person-years. For those who have never used ADT the incidence was
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58 158 6.0/1000 person-years. Type 2 diabetes Incidence for ADT users was 8.8/1000 person-years,
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60 159 for men on GnRH agonists 9.0/1000 person-years and 5.8/1000 person-years for men on
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160 160 antiandrogens (**Table 2**).

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3 161 There was a significantly increased risk of developing of type 2 diabetes comparing ADT users
4 with ADT non-users (HR = 1.49, 95% CI = 1.34 to 1.66) (**Table 3**). Adjusted hazards models
5 162
6 163 for patient's age and tumour's stage also showed a statistically higher risk of developing type
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8 164 2 diabetes (aHR = 1.47, 95% CI = 1.32 to 1.64) in ADT users group. As compared to ADT
9 165 non-users the usage of GnRH agonists was associated with an increased risk of type 2 diabetes
10 166 (HR = 1.53, 95% CI = 1.38 to 1.71), however, there was no significant association between
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12 167 oral antiandrogen monotherapy and outcome.

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16 168 **Table 4** reports diabetes risk in the group of GnRH agonists users. There were no significant
17 169 differences in risk by duration of GnRH agonists exposure duration.

18 19 20 170 **4. Discussion**

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23 171 Our prostate cancer patient cohort study showed increased risk of diabetes in ADT users
24 172 compared to ADT-free patient cohort. In accordance with other studies, elevated risk was found
25 173 among GnRH agonist users, while in the antiandrogen monotherapy group no such increase
26 174 was observed.

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30 175 ADT, which decreases serum testosterone levels by inhibiting testosterone production, has
31 176 been the first line treatment for men with locally advanced or metastatic prostate cancer since
32 177 1940 [15]. ADT can reduce circulating testosterone levels to castration levels, however,
33 178 previous studies have shown that low levels of testosterone might decrease lean body mass
34 179 growth and increase fat deposition, also might cause insulin resistance by reducing insulin
35 180 sensitivity [16,17]. The association between ADT users in prostate cancer patients and insulin
36 181 resistance was identified in *Basaria et al.* study. Patients who received ADT for at least 12
37 182 months had an increased risk of developing insulin resistance and hyperglycaemia. Forty-four
38 183 percents of ADT patients had glucose levels in the diabetic range and the duration of ADT was
39 184 linked to the severity of these metabolic abnormalities [9]. *Bosco et al.* meta-analysis results
40 185 suggested that ADT usage for prostate cancer patients increased risk of diabetes by 36% [18].
41 186 In our study we also observed that ADT usage increases the risk of diabetes compared to ADT
42 187 non-users (HR: 1.49 95% CI 1.34 to 1.66).

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46 188 *Keating et al.* found that the treatment with GnRH agonists is associated with an increased risk
47 189 of type 2 diabetes compared to ADT non-users (HR for GnRH agonists versus no ADT: 1.44,
48 190 95% CI: 1.34 – 1.55) [5]. *Crawley et al.* evaluated the risk of type 2 diabetes for the patients
49 191 treated with GnRH agonists or antiandrogens. They found that GnRH agonists increase the risk

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3 192 of type 2 diabetes. In contrast management with antiandrogens was not associated with type 2
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5 193 diabetes [12]. In our study we showed the highest risk of diabetes was in GnRH agonists users
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7 194 group (HR: 1.53, 95% CI 1.38 to 1.71). This data is in line with above mentioned studies.
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10 195 The duration of ADT is a very important factor when trying to establish the link between type
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12 196 2 diabetes and ADT. *Keating et al.* showed increase risk of type 2 diabetes for patients on
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14 197 GnRH agonists, however, this study had a relatively short duration (up to 25 months) [5]. To
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16 198 our knowledge *Crawley et colleagues* were the first that evaluated different types of ADT and
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18 199 the effect of treatment duration. They examined the risk of type 2 diabetes with up to ten years
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20 200 of exposure. In their study they revealed that patients on GnRH agonists during the first 3 years
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22 201 (2 – 2.5 years of exposure HR: 1.68, 95% CI 1.40 to 2.02) had the highest risk of developing
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24 202 type 2 diabetes [12]. Similarly, we showed that the highest incidence of diabetes was in the 3-
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26 203 year-exposure group (HR: 1.77, 95% CI 1.44 to 2.18), however, the risk was also significantly
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28 204 elevated in other categories.

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30 205 Intermittent ADT treatment was suggested as alternative treatment to continuous ADT with
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32 206 possibly fewer complications and better quality of life [19]. *Rezaei et al.* study's results showed
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34 207 that in short-term treatment with intermittent ADT there was no difference in fasting blood
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36 208 glucose, which suggests lower risks of diabetes mellitus in this group of patients [20]. Thus,
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38 209 difference in diabetes risk increase between non-users and ADT users could be mitigated by
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40 210 the proportion of intermittent ADT user in our cohort, whom we could not identify from our
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42 211 database. However, according to general used prostate cancer treatment guidelines intermittent
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44 212 ADT could be applicable only for very small and well-informed fraction of prostate cancer
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46 213 patients [21]. Therefore, we consider that this should not influence the final results of our study.
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48 214 Large cohort size, population-based design and long observation time (up to 15 years) are
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50 215 strenghts of our study. Main limitation of our study is lack of clinical information regarding
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52 216 treatment modality, applied for patients in combination with ADT, especially information on
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54 217 surgical castration. This type of ADT is not common in clinical practice, therefore inclusion of
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56 218 those cases in non-ADT patients group has no substantial effect on diabetes risk evaluation.
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58 219 Another limitation is that differences in ADT treatment groups could be influenced by selection
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60 220 bias, as GnRH agonists are used for treatment of metastatic disease, however differences in
221 ADT treatment groups remains after adjusting to stage of disease.

222 5. Conclusion

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3 223 This study showed that there is increased risk of diabetes in prostate cancer patients treated
4 224 with ADT in comparison with ADT-free patient cohort. GnRH agonist users showed higher
5 225 susceptibility while the group on antiandrogen monotherapy showed no such increase.
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8 9 226 **Ethics approval**

10
11 227 This research was approved by Vilnius regional bioethics committee (Nr. 158200-16-879-388).
12 228 Bioethics committee waived off informed consent.
13
14

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17 231 not-for-profit sectors.
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20 232 **Competing interests**

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23 233 The authors declare no conflict of interest.
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25 234 **Contributorship statement**

26
27 235 Conceptualization, Mingaile Drevinskaite, Ausvydas Patasius and Giedre Smailyte; Planning,
28 236 Ausvydas Patasius, Marius Kincius, Vincas Urbonas, Giedre Smailyte; Data curation, Giedre
29 237 Smailyte; Formal analysis, Ausvydas Patasius and Giedre Smailyte; Methodology, Ausvydas
30 238 Patasius and Giedre Smailyte; Project administration, Giedre Smailyte; Resources, Giedre
31 239 Smailyte; Supervision, Giedre Smailyte; Writing – original draft, Mingaile Drevinskaite;
32 240 Writing – review & editing, Ausvydas Patasius, Marius Kincius, Vincas Urbonas and Giedre
33 241 Smailyte; Conception and design, Marius Kincius, Vincas Urbonas, Giedre Smailyte.
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40 242 **Data availability**

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43 243 Data are available upon reasonable request.
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48 245 **References**

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304 **Table 1** Baseline characteristics of men with prostate cancer by ADT use.

	All Patients	ADT Free Cohort	ADT users	AA	GnRH	p value*
n (%)	27580 (100%)	14502 (52.6%)	13078 (47.4%)	1014 (7.8%)	12064 (92.2%)	
Mean follow up time, years (SE)	6.74 (3.64)	6.54 (3.56)	6.97 (3.73)	7.12 (4.34)	6.95 (3.68)	
Age						
Mean age at diagnosis, years (SE)	67.81 (8.61)	68.71 (10.05)	66.81 (6.53)	66.10 (6.50)	66.87 (6.53)	<0.001
<65	9327 (33.9%)	5120 (35.3%)	4207 (32.2%)	374 (36.9%)	3833 (31.8%)	
65-74	12441 (45.1%)	4715 (32.5%)	7726 (59.0%)	580 (57.2%)	7146 (59.2%)	
>75	5812 (21.0%)	4667 (32.2%)	1145 (8.8%)	60 (5.9%)	1085 (9.0%)	
Stage						
I	1913 (6.9%)	1380 (9.5%)	533 (4.0%)	25 (2.5%)	508 (4.2%)	<0.001
II	11986 (43.5%)	6660 (45.9%)	5326 (40.8%)	460 (45.3%)	4866 (40.4%)	
III	7157 (25.9%)	2671 (18.4%)	4486 (34.3%)	214 (21.1%)	4272 (35.4%)	
IV	1461 (5.3%)	663 (4.6%)	798 (6.1%)	105 (10.4%)	693 (5.7%)	
Unknown	5063 (18.4%)	3128 (21.6%)	1935 (14.8%)	210 (20.7%)	1725 (14.3%)	

305 * shows significance of differences between the ADT free cohort and ADT users

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311 **Table 2** Incidence of type 2 diabetes per 1000 person-years in prostate cancer patients by ADT
 312 use

	Number of patients	Number of events	Person years	Incidence rate
All patients	27580	1371	185961,74	7.4
ADT non-users	14502	570	94866,21	6.0
ADT users	13078	801	91095,53	8.8
GnRH agonists users	12064	759	87683,91	9.0
Antiandrogen users	1014	42	3411,62	5.8

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314 **Table 3** Hazard ratios (HR) for type 2 diabetes in prostate cancer by use of ADT.

	HR	95% CI	aHR*	95% CI
ADT free cohort	ref.	-	ref.	-
ADT users	1.49	1.34 to 1.66	1.47	1.32 to 1.64
GnRH agonists users	1.53	1.38 to 1.71	1.51	1.35 to 1.69
Antiandrogen users	1.02	0.75 to 1.40	1.02	0.74 to 1.39

315 * adjusted for age and stage

316

317 **Table 4** Hazard ratios (HR) for type 2 diabetes in men with prostate cancer on GnRH
 318 agonists for different periods of exposure.

Years of exposure	Number of events	Number of patients	HR	95% CI	aHR*	95% CI
ADT free cohort	570	14502	ref.	-	Ref.	-
0–1	369	6800	1.41	1.23 to 1.61	1.38	1.21 to 1.58
1–2	139	2177	1.60	1.33 to 1.93	1.59	1.32 to 1.92
2–3	105	1330	1.77	1.44 to 2.18	1.76	1.42 to 2.17
3–5	96	1151	1.74	1.40 to 2.16	1.73	1.42 to 2.17
>5	50	606	1.58	1.18 to 2.11	1.57	1.17 to 2.10

319 * adjusted for age and stage

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract [Page 1; lines 1-2] (b) Provide in the abstract an informative and balanced summary of what was done and what was found [Page 2; lines 42-62]
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported [Page 3-4, lines 87-107]
Objectives	3	State specific objectives, including any prespecified hypotheses [Page 4, lines 106-107]
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection [Page 4, lines 110-117]
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up [Page 4-5, lines 118-134] (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable [Page 5, 136-140]
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Exposed and Unexposed group [Page 5, lines 141-147]
Bias	9	Describe any efforts to address potential sources of bias [Page 2, lines 68-70]
Study size	10	Explain how the study size was arrived at [Page 4, lines 130-134]
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why [quantitative variable - age]
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding [Page 5, lines 141-147] (b) Describe any methods used to examine subgroups and interactions [Cox proportional Hazard] (c) Explain how missing data were addressed [not applicable] (d) If applicable, explain how loss to follow-up was addressed [not applicable] (e) Describe any sensitivity analyses [not applicable]
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed [Page 5, lines 156-160] (b) Give reasons for non-participation at each stage [not applicable] (c) Consider use of a flow diagram [not applicable]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders [Page 5, lines 156-160] (b) Indicate number of participants with missing data for each variable of interest [not applicable]

		(c) Summarise follow-up time (eg, average and total amount) [Page 2, lines 64-65] [Page 6, lines 162-163]
Outcome data	15*	Report numbers of outcome events or summary measures over time [Page 6, lines 161-166]
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included [Page 6, lines 167-173 + Table 3. Adjusted to age and stage] (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period [not applicable]
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses [not applicable]
Discussion		
Key results	18	Summarise key results with reference to study objectives [Page 6-7, lines 177-227]
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias [Page 7-8, lines 220-227]
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence [Page 7-8, lines 177-227]
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based [Page 3, lines 72-74]

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.