



GPRD Study of GnRH analogues and depression/suicide

Provision of Final Report to Regulatory Authorities

17 December 2010

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1.0 INTRODUCTION

Leuprorelin is a synthetic nonapeptide analogue of gonadotropin-releasing hormone (GnRH), leuprorelin acetate, which possesses greater potency than the natural hormone. Following an initial stimulation, chronic administration of leuprorelin acetate results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid secretion. This effect is reversible upon discontinuation of drug therapy.

Administration of leuprorelin acetate results in an initial increase in circulating levels of gonadotrophins, which leads to a transient increase in gonadal steroid levels in both men and women. Continued administration of leuprorelin acetate results in a decrease of gonadotrophin and sex steroid levels.

Indications for use of leuprorelin include prostate cancer, endometriosis, uterine fibroids, *in-vitro* fertilisation and, in some countries, central precocious puberty and breast cancer.

2.0 BACKGROUND

A potential signal of suicidal reactions arose from a query from a Japanese academic centre following their survey in women with uterine fibroids receiving gonadotrophin releasing hormone analogues. As a result, Takeda proposed to carry out a pharmacoepidemiological study of the risk of suicide and severe depression in patients treated with these drugs. This proposal was submitted to the regulatory authorities in Europe. Takeda received multiple suggestions from various regulatory authorities on the study design and these were discussed with the agencies and the majority were included in the final protocol. The key change introduced through the regulatory interaction was that the study design originally developed to consider the different female populations treated with GnRH analogues was extended, following Medicines and Healthcare products Regulatory Agency (MHRA) request, to include male patients treated for prostate cancer.

The final results of this study have now been provided to Takeda by the General Practice Research Database (GPRD) research team. Whilst the results of the study do not suggest any increase in the risk of depression or suicide in the different female populations, an unexpected signal of an increased risk of suicide has been detected in one of the analyses in the prostate cancer population treated with GnRH analogues.

3.0 STUDY DESIGN

Given the range of indications and treatment populations the study design incorporated cohort and nested case control analyses, using two different population definitions in order to try to identify any confounding by indication.

Definition 1

Patients prescribed GnRH for the first time in GPRD for any indication (study population 1), and control patients with no record of prostate cancer, endometriosis or uterine fibroids and no prescription for GnRH analogues, matched by age, sex, calendar year and practice (study population 2).

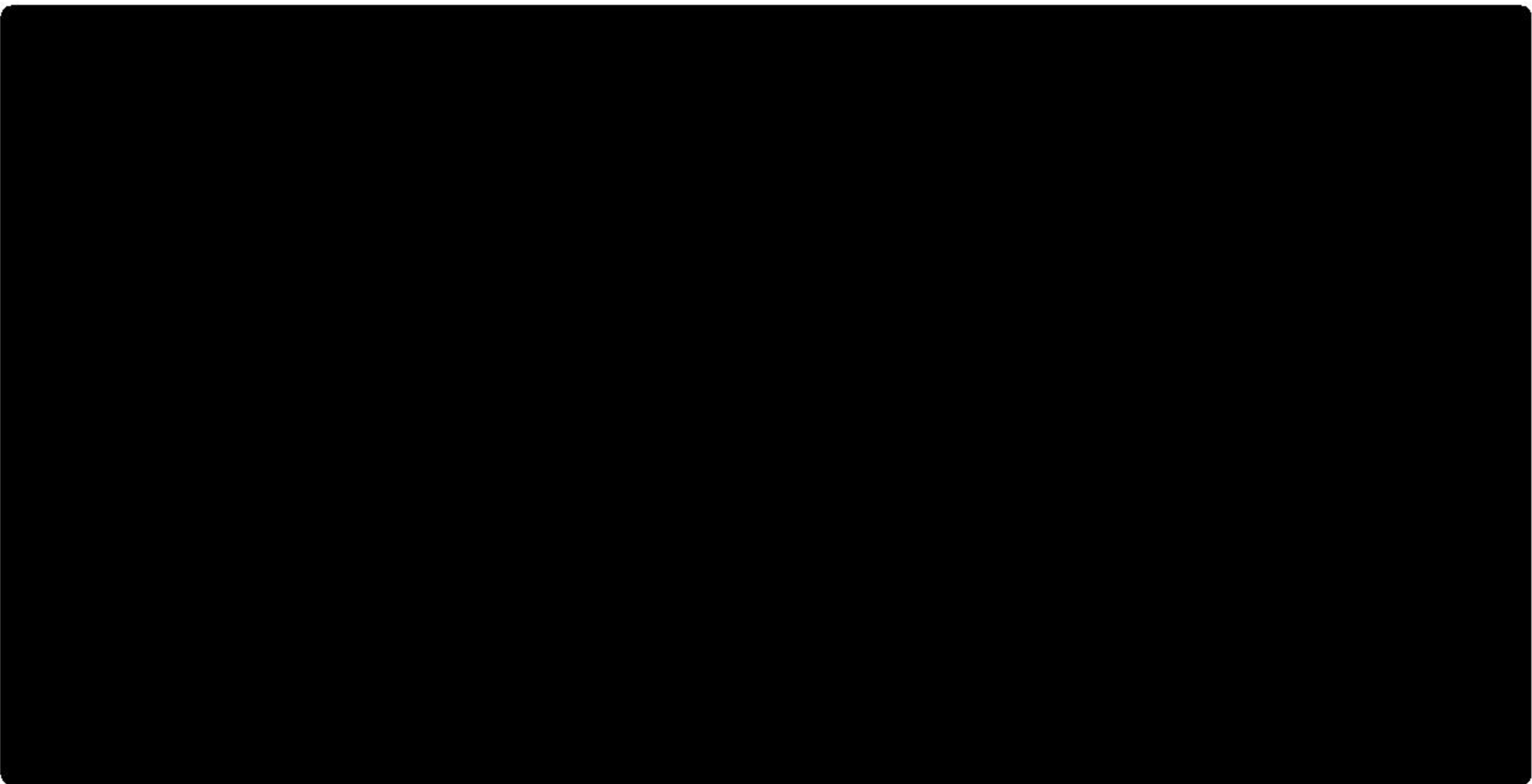
Definition 2.

Patients with an indication for GnRH treatment (namely endometriosis, uterine fibroids or prostate cancer) but without a prescription for GnRH treatment (study population 3), and control patients matched with no record of prostate cancer, endometriosis or uterine fibroids and no prescription for GnRH analogues, by age, sex, calendar year and practice (study population 4).

The study population identified using definition 2 was used to identify underlying co-morbidities in the various sub populations. This analysis was designed to assess the potential for confounding by indication and uses non-exposed patients. Patients were censored when they started GnRH therapy and were then eligible for inclusion in study population 1.

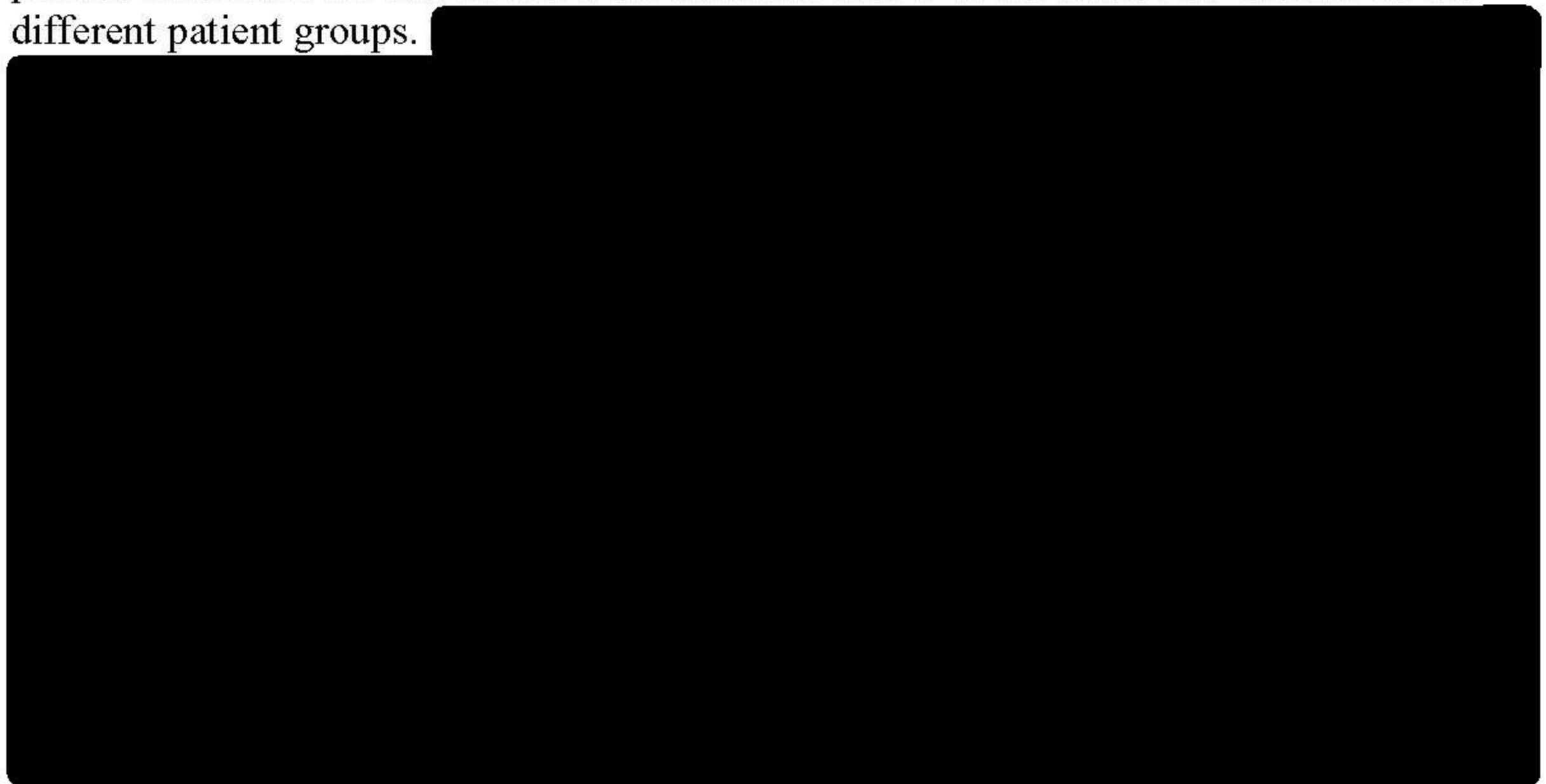
The analyses were stratified by indication in order to address the fact that confounders were likely to act to a different extent in the different populations. Furthermore, analyses were carried out within each population comparing GnRH exposed patients to unexposed patients and to patients with past exposure. Patients with past exposure are likely to return to baseline status and therefore provide a useful comparator population likely to suffer from less unmeasured confounding by indication.

4.0 STUDY RESULTS



5.0 DISCUSSION

The GPRD study was initially designed to investigate whether there was an increased risk of depression and suicide during treatment for endometriosis or uterine fibroids with GnRH analogues. Subsequently the study was expanded to include patients with prostate cancer and the analyses were stratified by indication in order to try to control for different patient characteristics and to allow for different effects of the same confounders in the different patient groups.



6.0 LITERATURE REVIEW

Takeda has carried out a literature review to see whether there is any relevant information in the scientific literature on the risk of depression and suicide in patients with prostate cancer treated with GnRH analogues. A summary of the key findings, rather than the entire literature, is provided below.

A case series reported by Rosenblatt and Mellow in 1995 (Rosenblatt 1995), looked at 3 prostate cancer patients with risk factors for depression, who experienced depression after starting leuprorelin injections for advanced prostate cancer. All patients experienced positive dechallenge, and two patients experienced positive rechallenge. The authors conclude that whilst GnRH analogues are useful treatments for advanced prostate cancer, the primary care physician should be alert to a possible onset of depression, particularly in patients with a history of depression

A study by Cherrier et al (Cherrier, Aubin et al. 2009) looked at cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. This study comprised twenty hormone naive, eugonadal prostate cancer patients without evidence of metastases and with a rising PSA treated with intermittent ADT consisting of 9 months of complete androgen blockade (CAB) achieved with combined leuprolide and flutamide followed by an 'off treatment' period, and twenty healthy controls. ADT patients evidenced a significant decline in spatial reasoning, spatial abilities and working memory during treatment compared with baseline, together with significant changes in self-rated mood such as increased depression, tension,

anxiety, fatigue and irritability. No significant changes in either cognitive tests or mood measures were noted for the healthy control group. These findings, suggest that 9 months of combined androgen blockade may result in some adverse changes in cognition and mood. However, many but not all of these changes can return to baseline after cessation of ADT.

A prospective study by Pirl et al (Pirl, Greer et al. 2008) examined the development of depressive symptoms and fatigue among men with locally advanced prostate cancer receiving hormone therapy. Fifty two men were randomly assigned to receive either parenteral leuprolide or oral bicalutamide. Patients completed the Beck Depression Inventory and Fatigue Severity Scale at pretreatment baseline, 6 months and 12 months. Rates of at least mild depression ranged from 10.4% to 16.3% over the 12 months and were not significantly different at each time point, either overall or within each treatment group. There were no significant differences between the groups, although the sample size was small.

Shahinian et al (Shahinian, Kuo et al. 2006) conducted a study using the US Medicare database. This study assessed the risk of physician diagnoses of depression, cognitive impairment, or constitutional symptoms in a sample of 50 613 men with incident prostate cancer and 50 476 men without cancer, from 1992 through 1997, using the linked Surveillance, Epidemiology, and End Results - Medicare database. Cox proportional hazards regression was used to adjust for confounding variables. In men surviving at least 5 years after diagnosis, 31.3% of those receiving androgen deprivation developed at least 1 depressive, cognitive, or constitutional diagnosis compared with 23.7% in those who did not ($P < .001$). After adjustment for variables such as comorbidity, tumour characteristics, and age, the risks associated with androgen deprivation were substantially reduced or abolished: relative risk (RR) for depression diagnosis, 1.08 (95% confidence interval [CI], 1.02-1.15); RR for cognitive impairment, 0.99 (95% CI, 0.94-1.04); and RR for constitutional symptoms, 1.17 (95% CI, 1.13-1.22). The authors concluded that depressive, cognitive, and constitutional disorders occur more commonly in patients receiving androgen deprivation, but this appears to be primarily because patients receiving androgen deprivation are older and have more comorbid conditions and more advanced cancers.

Chism and Kunkel (Chism and Kunkel 2009) reviewed the available evidence on the psychiatric and social impact of the diagnosis and treatment of prostate cancer and concluded that the treatment paradigm for metastatic disease uniformly begins with androgen deprivation therapy (ADT). They report one study of men receiving ADT which found an incidence of de novo psychiatric illness approaching 30%. The most commonly identified illnesses in this cohort of 395 men were depression, dementia, and anxiety. The authors considered that the higher incidence of psychiatric illness in this population, as compared with men with more localized illness, likely results from greater disease burden, as well as from the increased risk of depression and dementia with advancing age.

A report from Wassersug (Wassersug 2007) compares the motivations for and responses to chemical castration in patients being treated for prostate cancer and “voluntary

modern-day eunuchs". They note that most voluntary eunuchs function well psychologically and socially, and do not appear to suffer from ADT induced depression. Their conclusion is that motivation rather than physiology appears to account for the different responses to ADT. A report by Giltay (Giltay and Gooren 2009) considered the potential side effects of androgen deprivation treatment in sex offenders. Whilst this is not a licensed indication, this report is of interest because the demographic and disease co-morbidity profile of the subjects is different from prostate cancer patients. However, this report is simply referencing the known side effect profile of ADT as reported in product characteristics and summarising effects seen in other studies including Shahinian et al.

7.0 CONCLUSION

8.0 REFERENCES

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Appendix 1- GRPD study Protocol



The Risk of Depression and Suicidal Behaviour Among Patients Treated with Gonadotropin Releasing Hormone (GnRH) Agonists.

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Date of protocol: March 2, 2010

This protocol is a substantial revision of protocol 08-078 previously approved by ISAC. This protocol was modified following comments by regulatory authorities. The GPRD research Team will now undertake the research.

LAY SUMMARY

Endometriosis is a medical condition of the womb in women. Womb cells appear and flourish in areas outside the womb, which can lead to severe pain in the lower abdomen. Gonadotropin-releasing hormone (GnRH) agonists (goserelin, leuprorelin, triptorelin, buserelin, nafarelin) are prescribed to women with this condition. There have been some reports that these medicines may have side-effects and increase the risk of depression (feeling 'blue'). There are even reports that suggest that these medicines may lead to women committing suicide. The difficulty is that endometriosis itself can be a severe condition and may lead to depression or suicide itself. The current GPRD study will attempt to study whether GnRH medicines are associated with depression.

BACKGROUND

Gonadotropin-releasing hormone (GnRH) agonists (goserelin, leuprorelin, triptorelin, buserelin, nafarelin) are prescribed to women for treatment of endometriosis (Schweppe et al 2005). The agents desensitize GnRH receptors of the pituitary gland under continued exposure, which causes an initial stimulation of the pituitary–ovarian axis, followed by a reduction in circulating serum gonadotropin concentration and inhibition of ovarian function (Shaw 1992). While GnRH agonists reduce the extent of endometrial lesions and occurrence of pelvic pain associated with endometriosis, the drug class is associated with physical and psychiatric side effects generally related to the reduction in plasma concentration of estrogens and testosterone (Warnock et al 1998). The label for leuprorelin (Leuprolide, TAP Pharmaceuticals, 1995) lists depression/emotional lability as adverse event that occurs in approximately 23% of patients treated for 6 months. In a study of 411 women treated with goserelin (Zoladex) for endometriosis, the following adverse psychiatric events were noted: depression, 54%; emotional lability, 60% and decreased libido, 61% (Zeneca Pharmaceuticals, 1995). Add back therapy is used to relieve the side effects of GnRH agonists, in which various steroid agents are combined with GnRH agonist therapy and has been recommended as a means of maintaining a therapeutic response and preventing potential adverse effects of GnRH agonist treatment (Lindsay et al., 1996) in endometriosis patients (Hornstein et al 1998).

Recently, GnRH agonists have been associated with cases of suicide in women. The Japan Endometriosis Association (JEMA) routinely conducts a national endometriosis survey every five years. Data from 668 endometriosis patients collected in 2006 showed that 28% of respondents suffered depression whilst using GnRH-agonists with 16% having suicidal thoughts and 2% actually attempted suicide (Japanese Endometriosis Association, 2007).

Whilst endometriosis is a disorder with a prevalence rate of 5-10% in the general population (Lu and Ory 1995), depression in women diagnosed with endometriosis is very common, e.g. depression requiring medication or medical consultation in women with endometriosis found to be 33% (Sinaii et al 2008). Another study compared prevalence of depression in women in general population and women diagnosed with endometriosis (Mirkin et al 2007). The difference was statistically significant with a prevalence of depression of 3.9% vs. 6.8% (p-value<0.001). Depression in patients with endometriosis is also clearly associated with presence of chronic pelvic pain: 52% of patients suffering from pelvic pain were moderate to severely depressed. Similar results were found in other studies (Lorenatto et al 2006).

Suicidal ideation and attempts are strongly associated with prevalence of depression: more than 80% of suicide attempts are linked to comorbid psychiatric disorders, most commonly depression (Henriksson et al 1993). According to WHO, the total rate of depression is higher in females than males whilst the rate of suicide attempts in males is 2-fold higher than in females (WHO).

The linkage between diagnosis of endometriosis, depression and treatment with GnRH agonists is complex. Steingold et al 1987 noted that 12 of 16 treated patients (75%) suffered from depression while receiving GnRH agonist therapy. Three of the twelve patients also complained of concomitant irritability/anxiety. For two subjects (13%), the psychiatric symptoms were severe enough to discontinue GnRH agonist therapy. In another study, Warnock et al (1998) described that 16 of 20 women with laparoscopically diagnosed endometriosis were treated for 24 weeks with GnRH agonist therapy and developed significant depressive symptoms. In addition, four case reports indicated that anxiety and mood symptoms occurred in women with endometriosis having no prior psychiatric history that were treated with GnRH agonists. These women developed symptoms consistent with various psychiatric disorders, including panic disorder and major depression with and without psychotic features (Warnock and Bundren, 1997). In order to investigate the association between treatment with GnRH agonists and depression and suicide, a study will be conducted using data from the General Practice Research Database (GPRD).

OBJECTIVES

1. To describe the prescribing and drug-utilization of GnRH agonists in the GPRD
2. To estimate the incidence rates of depression and suicidal behaviour in patients using GnRH agonists stratified by indication for treatment and exposure characteristics
3. To estimate the incidence rates of depression and suicidal behaviour in patients with the indication for treatment but untreated with GnRH agonists in GPRD

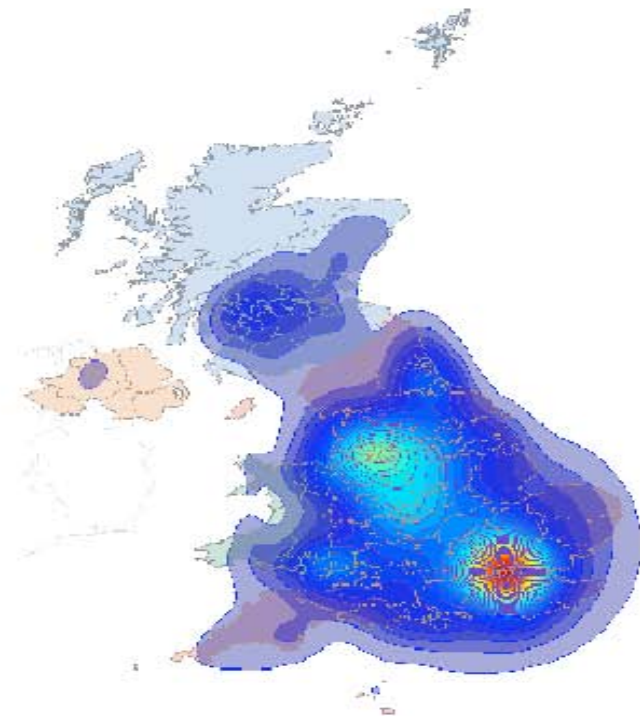
4. To estimate the relative risk of depression and suicidal behaviour in users of GnRH agonists.
5. To identify the risk factors associated with the development of depression and suicidal behaviour in patients with endometriosis prescribed GnRH agonists.

DATA SOURCE

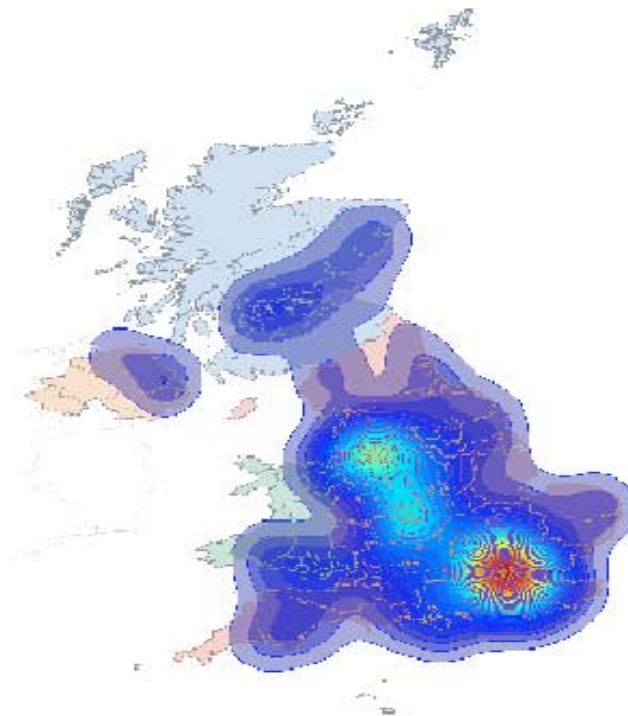
Data for this study will be obtained from the General Practice Research Database (GPRD). GPRD collates the computerized medical records of general practitioners (GPs). GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Patients are semi-permanently affiliated with a practice that centralizes the medical information from the GPs, specialist referrals, and hospitalizations. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes [www.gprd.com]. Several software packages are used by GPs for their patients' medical records, including Vision from In Practice Systems Ltd and EMIS that combined cover just over 80% of all UK practices. The GPRD currently contains the complete anonymised patient medical records from GPs who use the system from In Practice Systems and who agree to adhere to "Recording Guidelines" that are subjected to detailed quality control checks of data at both practice and individual patient level. Figure 1 shows the population density and the distribution of GPRD practices across the UK.

Figure 1: Population density of UK population and coverage of GPRD (smoothed estimates)

Population density of UK population



Coverage of GPRD



GPRD can now be linked individually and anonymously to other NHS datasets in England (appropriate approvals have been obtained for this; only the GP will know the patient's name and address and investigators will have no access to these patient identifiers). Currently, 200 GP practices in England are participating in this linkage (about 40% of GPRD) and GPRD is actively recruiting practices for this linkage and is expected to increase later this year. Data from the Hospital Episode Statistics (HES) and National Death Certificates (with date and primary and secondary cause of death) will be used for this study. Participating GP practices send information on patient identifiers (including NHS number) and the anonymous GPRD patient number to a trusted third party. The linked database also sends information on patient identifiers and their patient numbers to the trusted third party. After matching, the patient identifiers are removed and GPRD is then linked anonymously to other databases. The HES consist of two registries: (i) inpatient HES with all NHS hospitalisations (including date of admission and discharge, main diagnoses and main procedures) and (ii) outpatient HES with dates of outpatient consultations (diagnostic information in outpatient HES is incomplete).

STUDY DESIGN

The study design will be a retrospective cohort design with nested case control study using data from 1990 onwards. The type of study will be hypothesis testing.

STUDY POPULATIONS INCLUDING COMPARISON GROUPS

The following study populations will be identified:

1. patients prescribed GnRH for any indication
2. control patients matched by age, sex, calendar year and practice
3. patients with an indication for GnRH treatment (such as endometriosis, uterine fibroids or prostate cancer)
4. control patients matched by age, sex, calendar year and practice

Appendix I lists the various GnRH treatments and indications. The first two populations will be used to evaluate the primary objective of evaluating the association between GnRH exposure and depression or suicidality. These analyses will be stratified by indication, age and sex. The last two populations will be used to evaluate the contribution of underlying disease to the outcomes and to attempt to quantify the magnitude of possible bias in the analysis of the primary objective.

EXPOSURE

The study population prescribed GnRH will be stratified by indication for treatment. In this population, the date of the first GnRH prescription during the period of GPRD data collection will be defined as the index date. In the population of patients with an indication for GnRH treatment, the index date will be the first record of the indication in 2000 onwards. Each patient in these two populations will be matched to three control patients by age, sex, practice and calendar time (i.e., same index date). The period of follow-up will be from the index date up to latest GPRD data collection, patient's transfer out of the practice, or patient's death, whichever date comes first. Exposure to GnRH will be classified in a time-dependent manner. Current exposure of GnRH will be the period of time from the first day of a prescription going forward for 40 days for a 1M agent or 118 days for a 3M agent. If another GnRH agonist is received person time will continue to be accumulated as current exposure, unless a gap of greater than 10 days from the end of current use occurs. If the gap occurs, then recent exposure time will be accumulated for next 30 days for 1M and 3M agent. Past use will then be accumulated for more than 70 days for 1M agent and more than 148 days for 3M agent. Any time a new GnRH agonist prescription is received current exposure will again be accumulated as described above. Time will be accumulated until a study patient becomes a case, leaves the practice, dies or end of data collection, whichever comes first. It will be noted if prescriptions are given within the first year of GPRD data collection. We will further assess whether any of the patients received GnRH agonists as monotherapy or in combination with add back therapy.

Evaluation of exposure misclassification

Use of GnRH for the indication of infertility treatment is unlikely to be recorded. This may lead to exposure misclassification (as discussed previously). In order to determine the extent of this misclassification bias, the GPRD free-text of control patients will be searched for the mention of GnRH prescribing (goserelin, leuprorelin, triptorelin, buserelin, nafarelin or their trade names). Free text consists of text entered by GPs or electronic letters as received from hospitals pasted into the free-text.

The extent of free-text data entry varies between GPs and practices. In order to better describe the likelihood of recording of outcomes in free-text, the average amount of free-text (number of characters) per patient will be estimated for each practice stratified by calendar time (based on all GPRD data). Based on the changes in average amount of free text over calendar time, a starting

year will be selected. Practices will then be ranked by the average amount of free-text overall. In practices above the median average amount of free-text, we will compare the number of patients prescribed GnRH identified in free-text to those with prescription records of GnRH.

SAMPLE SIZE

The number of patients prescribed goserelin, leuprorelin, triptorelin, buserelin, or nafarelin in November 2009 is as follows (restricting to acceptable patients aged 18+ who received a GnRH prescription during GPRD collection:

	No restriction	At least 1 year after GPRD start data collection
Goserelin	27,259	22,054
Leuprorelin	6,977	5,841
Triptorelin	792	714
Buserelin	2,336	1,724
Nafarelin	2,078	1,647
ALL	36,959	29,668

24,952 patients with a clinical or referral record of endometriosis have been identified in GPRD database. Of these, 2,892 patients have a subsequent first ever prescription of GnRH agonists (as specified in section 6.7.2 of the BNF). Of these, 345 have a subsequent first ever clinical or referral record of depression / suicidal behaviour.

OUTCOMES

The following five sources will be used to assess outcomes:

- (i) GPRD Read codes as recorded by the GPRD practice
- (ii) Prescription records as prescribed by the GP
- (iii) Free-text. This will be searched for text strings such as 'suicide' (a detailed list will be developed for the amended protocol). Free text consists of text entered by GPs or electronic letters as received from hospitals pasted into the free-text. The extent of free-text data entry varies between GPs and practices.

- (iv) Inpatient Hospital Episode Statistics (HES) with hospitalisations (this data source only records events that lead to hospital admission with the patient being alive). GPRD is now linked for about 40% of GPRD patients to HES in England.
- (v) Death certificates. GPRD is now linked for about 40% of GPRD patients to the official death certificates in England.

The following incident outcomes will be measured in this study:

- (i) Suicide (recorded in GPRD with Read codes, as outlined in Appendix II, or GPRD free-text, to be defined in detail).
- (ii) Suicide as cause of death (recorded on death certificates)
- (iii) Incident depression (recorded in GPRD with Read codes and prescriptions for antidepressants). Cases will be patients with a record of a GP visit for depression (see Appendix III for Read codes) or prescribing of antidepressants (see Annex 6).
- (iv) Admission to hospital due to depression (recorded in HES)

The following patients will be excluded from the analyses of all outcomes: patients with a history of suicide attempts, alcoholism or drug abuse, severe mental illness (such as schizophrenia, bipolar disorder, dementia, personality disorder or schizoaffective disorder). The following patients will be excluded from the analysis of incident depression in GPRD (but included in the analyses for suicide and hospital admission for depression and considered as covariate): patients with a history of depression or prescription for antidepressants at any time before the index date (i.e. first prescription of GnRH). The rationale for these exclusions is that *exacerbations* of depressions are difficult to measure in GPRD. Therefore, the focus will be on the development of *incident* disease. As an example of our approach, patients with a history of depression prior to the first GnRH prescription will be excluded from the depression analysis but included in the suicide analysis (and the depression history noted as a covariate).

A sensitivity analysis will be conducted for the GPRD depression outcome. In this analysis, patients with a past history of depression or treatment for depression more than 2 years prior to the index date will also be included.

COVARIATES

The following risk factors will be investigated as potential confounders:

- (i) age

- (ii) body mass index, smoking and alcohol use history
- (iii) calendar year
- (iv) season
- (v) Small-area socioeconomic class
- (vi) Number of GP visits (for any reason) in the 6 to 12 months before
- (vii) Recent prescribing of oral corticosteroids, benzodiazepine, NSAIDs or Cox-2 inhibitors, MST buprenorphine / fentanyl patches, tramadol, codeine, other opioid analgesics, hormonal therapeutics (progesterone, progestins; danazol/ gestrinone), oral contraceptives, aromatase inhibitors
- (viii) History of co-morbidities: Diabetes mellitus, cerebrovascular disease, ischaemic heart disease, congestive heart failure, peripheral vascular disease, hypertension, Parkinson's disease, restless legs syndrome, fibromyalgia, COPD, asthma, urinary problems (kidney disease, prostate problems) and gastrointestinal problems (e.g. IBS, ulcers)
- (ix) history of depression (in suicide analyses)
- (x) history of laparoscopy
- (xi) sterility
- (xii) duration of indication for treatment

ANALYSES

The study will consist of four major parts:

PART I CHARACTERISTICS OF STUDY POPULATION

Baseline characteristics

This analysis will describe the patient characteristics of the study population of GnRH users and their matched controls at the index date, including the underlying disease.

Current exposure characteristics

This analysis will describe the current exposure characteristics of GnRH medication and evaluate how GnRH medications are used in actual clinical practice in the UK (and whether confounding by

exposure characteristics may occur). One GnRH prescription will be randomly selected for each study patient

PART II EVALUATION OF POTENTIAL BIASES IN EVALUATING DRUG EFFECTS

Confounding by underlying disease severity

This part of the study will evaluate the associations between the risk of the various outcomes and indication for GnRH treatment in the study population of patients with GnRH indication and their matched controls. Study patients will be followed for each of the outcomes from the disease index date up to date of death, patient leaving the practice or end of GPRD data collection, whichever date comes first. Time with current or recent exposure to GnRH will be excluded. The analyses will be stratified by type of indication for GnRH treatment.

Confounding by past exposure characteristics

This analysis will evaluate the extent of confounding by past exposure characteristics by estimating the risk of the each of the outcomes stratified by the various exposure characteristics in past GnRH users. This analysis will include past exposure periods of GnRH users and the follow-up time of their control patients. This analysis will include all variables as listed in the section on ‘current exposure characteristics’ but will be restricted to the period of past exposure. Poisson regression will be used. The analyses will be stratified by type of indication for GnRH treatment.

PART III RELATIVE RATES OF OUTCOMES WITH GnRH EXPOSURE

Relative rates of outcomes during current GnRH exposure

This part of the study will compare GnRH users for the risk of various outcomes during current exposure compared to past exposure and compared to non-use in matched control patients. The exposure of patients will be classified in a time-dependent manner, as outlined above. Poisson regression models will be used. These models will also include age, gender and the potential confounders. The analyses will be stratified by type of indication for GnRH treatment.

Nested case-control study

In order to more carefully control for calendar time, two nested case-control analyses in the cohort of GnRH agonist users will be conducted; 1) treated depression 2) suicidal behavior. A total of four controls per case will be matched on year of birth, practice, year of registration in the GPRD and index date. A control must have never been diagnosed with 1) treated depression and/or suicidal behavior 2) and must be present in the database at the index date. Conditional logistic regression will be used to calculate odds ratios.

PART IV DESCRIPTION OF THE HAZARD RATES OF OUTCOMES

This part of study will only be conducted in case of clinically relevant findings of increased risks with GnRH.

Patterns of hazard rates over time

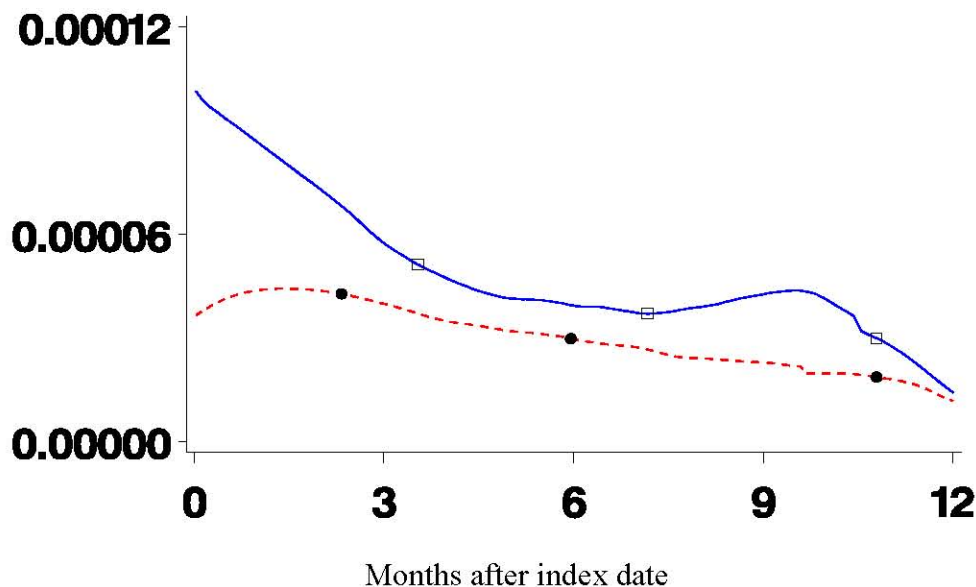
This part of the study will describe the patterns of hazard rates of various outcomes over duration of treatment or control follow-up. This approach has been used in previous studies of asthma medication (Zhang et al. 2009). This pattern analysis will focus on convergence/divergence of hazard rates rather than on estimating relative rates (RRs). If two hazard rates that are substantially different but remain parallel with changes in exposure, this pattern analysis would suggest a lack of differential effects.

We will estimate the hazard rates (i.e., absolute risk) over time following the index date for the frequent major adverse safety outcomes. The hazard rates will be estimated by dividing the follow-up time into 100 periods and by calculating the absolute rate within each small period (the hazard rate provides the risk of the outcome over a small period of time). These estimates will then be smoothed using the methods proposed by Ramlau-Hansen [Ramlau-Hansen H, 1983]. This analysis of hazard rates displays visually the observed (crude) risks over time. This hazard analysis will be a descriptive analysis of the various event rates over time, describing the patterns over time. We will evaluate the *pattern* of hazard rates, assessing whether the hazard rates of different groups of patients remained parallel over time or whether they diverged/converged. We will evaluate whether hazard rates vary over time between various types of GnRH medication. This technique has been used by Gallagher et al. to evaluate, within the exposed cohort only, the differential effects of

bisphosphonates on hazard rates of osteoporotic and non-osteoporotic fractures (Gallagher et al. 2008). Figure 1 provides an example of this pattern analysis:

Figure 1 (□=drug A; ●=drug B)

Hazard rate



In this pattern analysis, *systematic* differences between two groups due to confounding are not a concern, as the analysis focuses on convergence/divergence of hazard rates rather than on estimating relative rates. In case of two rates that are substantially different but that remain parallel, this pattern analysis would find a lack of effect while the standard epidemiological analysis would find an increased relative rate. However, *time-dependent* confounding (i.e., differential changes in the comparison groups over time) is a concern with the pattern analysis as with standard epidemiological analyses. The approach to deal with this is to assess whether the characteristics of patients stopping treatment differentially change over time.

It will be evaluated whether the patterns of the hazard rates were proportional over time (i.e., whether the relative differences between hazard rates remained stable over time using a test for proportionality) [Zhang et al 2009]. The test for proportionality will be done using Cox proportional hazards analysis testing the interaction between the relative rate and time since the index date. These analyses will be stratified by age, gender, and GnRH indication.

LIMITATIONS OF THE STUDY

As in any observational study, confounding by indication is of major concern. Women diagnosed with severe symptoms of endometriosis may be more likely to be treated with GnRH agonists and at higher risk of severe depression. It may be possible that underlying diseases/ co-morbidities associated with depression and suicide are undetected at the time of the first GnRH agonist prescription. If the results show an increased risk of newly diagnosed and treated depression in users of GnRH agonists, it may be difficult to evaluate a causal association. Furthermore, GPRD does not capture any prescribing by consultants. However, in the UK the treatment of most chronic conditions (such as endometriosis) is typically referred back to the GP, which is captured in GPRD. Short-term treatments (for e.g. infertility) may not be captured in GPRD. The main effect of missing some exposed patients is that the patients in the control group are misclassified with respect to exposure status. However, this effect of this misclassification is likely to be small given the low prevalence of use. Another limitation will be that there will be incomplete information on some of the risk factors for suicide and depression and that we will be unable to determine exacerbation of depression.

DISSEMINATION OF STUDY RESULTS

It is expected that the results of this study will be published in a peer-reviewed journal.

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Appendix I

Drug	Proprietary Name (®)	Presentation	Indication(s)	Dose	Administration	Maximum treatment duration
Goserelin	Zoladex	3.6 mg subcutaneous (SC) implant	1) Endometriosis 2) Endometrial thinning 3) Uterine fibroids 4) Prostate cancer 5) Assisted reproduction 6) Breast cancer	3.6 mg once every 28 days	SC injection into the anterior abdominal wall	1) 6 months 2) 8 weeks 3) 3 months
Leuprorelin	Prostap SR	3.75 mg vial plus pre-filled diluent syringe	1) Endometriosis 2) Endometrial thinning 3) Uterine fibroids	3.75 mg once monthly	SC or intramuscular (IM) injection	1) 6 months 2) stat dose 3) 6 months
Leuprorelin	Prostap 3	11.25 mg vial plus pre-filled	1) Endometriosis 2) Prostate cancer	11.25 mg once every three	IM injection	6 months

		diluent syringe		months		
Triptorelin	Decapeptyl SR	3.0 mg vial with diluent	1) Endometriosis 2) Uterine fibromyoma 3) Prostate carcinoma 4) Female infertility	3.0 mg once every 28 days	IM injection	6 months
Triptorelin	Decapeptyl SR	15 mg vial with diluent	1) Endometriosis 2) Prostate cancer 3) Precocious puberty	11.25 mg once every three months	IM injection	6 months
Buserelin	Suprefact® injection ⁷	1.0mg multidose vial with diluent	1) Prostatic carcinoma	0.5ml at 8 hourly intervals for 7 days. On 8 th day treatment is changed to nasal spray	SC injection	6 months
Buserelin	Suprecur Nasal Spray	10g vial and nebuliser	1) Prostatic Carcinoma	100 µg six times daily	Nasal spray	6 months

Buserelin	Suprecur Nasal Spray	10g vial and nebuliser	1) Endometriosis 2) Infertility	1) 300 µg thrice daily 2) 150 µg four times daily	Nasal spray	6 months
Nafarelin	Synarel 2m	g/ml solution with metered spray pump	1) Endometriosis 2) Infertility	1) 200 µg twice daily 2) 400 µg twice daily	Nasal spray	6 months

Appendix II READ and OXMIS-codes to identify suicide

U2...13	[X]Suicide
TK...00	Suicide and selfinflicted injury
TK...14	Suicide and self harm
TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances
TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic
TK01.00	Suicide + selfinflicted poisoning by barbiturates
TK01000	Suicide and self inflicted injury by Amylobarbitone
TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic
TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines
TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS
TK06.00	Suicide + selfinflicted poisoning by agricultural chemical
TK07.00	Suicide + selfinflicted poisoning by corrosive/caustic subst
TK0z.00	Suicide + selfinflicted poisoning by solid/liquid subst NOS
TK1..00	Suicide + selfinflicted poisoning by gases in domestic use
TK10.00	Suicide + selfinflicted poisoning by gas via pipeline
TK11.00	Suicide + selfinflicted poisoning by liquified petrol gas
TK1y.00	Suicide and selfinflicted poisoning by other utility gas
TK20.00	Suicide + selfinflicted poisoning by motor veh exhaust gas
TK21.00	Suicide and selfinflicted poisoning by other carbon monoxide
TK3..00	Suicide + selfinflicted injury by hang/strangulate/suffocate
TK30.00	Suicide and selfinflicted injury by hanging
TK31.00	Suicide + selfinflicted injury by suffocation by plastic bag
TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
TK3z.00	Suicide + selfinflicted inj by hang/strangle/suffocate NOS
TK4..00	Suicide and selfinflicted injury by drowning
TK5..00	Suicide and selfinflicted injury by firearms and explosives
TK51.00	Suicide and selfinflicted injury by shotgun
TK52.00	Suicide and selfinflicted injury by hunting rifle
TK6..00	Suicide and selfinflicted injury by cutting and stabbing
TK60.00	Suicide and selfinflicted injury by cutting
TK61.00	Suicide and selfinflicted injury by stabbing

TK6z.00 Suicide and selfinflicted injury by cutting and stabbing NOS
 TK7..00 Suicide and selfinflicted injury by jumping from high place
 TK70.00 Suicide+selfinflicted injury-jump from residential premises
 TK72.00 Suicide+selfinflicted injury-jump from natural sites
 TK7z.00 Suicide+selfinflicted injury-jump from high place NOS
 TKx..00 Suicide and selfinflicted injury by othermeans
 TKx0.00 Suicide + selfinflicted injury-jump/lie before moving object
 TKx0000 Suicide + selfinflicted injury-jumping before moving object
 TKx1.00 Suicide and selfinflicted injury by burns or fire
 TKx2.00 Suicide and selfinflicted injury by scald
 TKx4.00 Suicide and selfinflicted injury by electrocution
 TKx5.00 Suicide and selfinflicted injury by crashing motor vehicle
 TKxy.00 Suicide and selfinflicted injury by other specified means
 TKxz.00 Suicide and selfinflicted injury by other means NOS
 TKz..00 Suicide and selfinflicted injury NOS
 SL...15 Overdose of drug
 TK...11 Cause of overdose – deliberate
 3009D Suicide
 1B19.00 Suicidal ????
 1B19.11 Suicidal – symptom suicide
 1BD..00 Harmful thoughts
 1BD2.00 Morbid thoughts
 1BD1.00 Suicidal ideation
 1BD3.00 Suicidal plans
 1BD4.00 Suicide risk
 TK...15 Attempted suicide
 TK...17 Para-suicide
 U2...14 [X]Attempted suicide
 U2...15 [X]Para-suicide
 TKy..00 Late effects of selfinflicted injury
 TK...11 Cause of overdose - deliberate
 TK...12 Injury - self-inflicted
 TK...13 Poisoning - self-inflicted
 3009B SUICIDE RISK

3009BN IDEATION SUICIDAL
3009BP PLANS SUICIDAL
3009BT SUICIDAL THOUGHTS
L3009DW DEATH - WISH FOR
3009J THOUGHTS MORBID
3009CT THREAT SUICIDAL
9779L DRUG OVERDOSE SUICIDAL
3009C ATTEMPTED SUICIDE
9947TC SUICIDE ATTEMPT STRANGULATION
L3009P PARASUICIDE
3009D SUICIDE
9779NA SUICIDAL OVERDOSE (DRUG)
3009IA VOLUNTARY EUTHENASIA
9947BC SUFFOCATION BEDCLOTHES
9947HN ASPHYXIA DUE HANGING
9947PB SUFFOCATION PLASTIC BAG
9947TA STRANGULATION ATTEMPTED
9947TR ASPHYXIA DUE STRANGULATION
9947TS STRANGULATION
9947TT SUFFOCATION STRANGULATION

Appendix III READ and OXMIS-codes to identify depression

GPRD Medical Code	Read / OXMIS Term
206611 Endogenous	depression
206719 [X]Depressive	episode, unspecified
206721 [X]Major	depression, recurrent without psychotic symptoms
215616	Endogenous depression - recurrent
215617	Recurrent major depressive episodes, severe, no psychosis
215666	Brief depressive reaction NOS
215710 [X]Recurrent	depressive disorder
215711	[X]Endogenous depression without psychotic symptoms
221414 Depressed	
224661 Agitated	depression
224662	Recurrent major depressive episode
224706	Brief depressive reaction
224749 [X]Depressive	episode
224750 [X]Prolonged	single episode of reactive depression
224751	[X]Recurrent episodes of reactive depression
233760	Single major depressive episode, moderate
233761	Recurrent major depressive episodes, unspecified
233777	Anxiety with depression
233831 Depressive	disorder NEC
233878	[X]Mild depressive episode
233879	[X]Severe depressive episode without psychotic symptoms
233880 [X]Depression	NOS
233881 [X]Depressive	disorder NOS
233883 [X]Recurrent	depressive disorder, unspecified
242927	[X]Single episode of depressive reaction
242930 [X]Recurrent	depressive disorder, current episode moderate
244686 [D]Postoperative	depression
248748	O/E - depressed
251968	Recurrent major depressive episodes, mild
251973 Masked	depression
252064	[X]Monopolar depression NOS

261171	Single major depressive episode
261172	Single major depressive episode NOS
261225 Chronic	depression
261276	[X]Single episode of psychogenic depression
261278	[X]Other depressive episodes
261279 [X]Vital	depression, recurrent without psychotic symptoms
261284	[X]Persistant anxiety depression
261287	[X]Mixed anxiety and depressive disorder
270430	Single major depressive episode, severe, without psychosis
270438 Agitated	depression
270540	[X]Single episode of reactive depression
270541	[X]Moderate depressive episode
270543	[X]Recurr depress disorder cur epi severe without psyc sympt
279511	Endogenous depression first episode
279512	Recurrent major depressive episodes, moderate
279602	[X]Single episode vital depression w/out psychotic symptoms
279603 [X]Atypical	depression
279604 [X]Recurrent	depressive disorder, current episode mild
288634	Endogenous depression first episode
288635	Single major depressive episode, unspecified
288636	Single major depressive episode, mild
288637	Recurrent major depressive episode NOS
288641	Atypical depressive disorder
297885 Recurrent	depression
297987	[X]Single episode agitated depressn w/out psychotic symptoms
297988	[X]Single episode major depression w/out psychotic symptoms
297989	[X] Reactive depression NOS
297996	[X]Mild anxiety depression
303346 DEPRESSION	AGITATED
303349 DEPRESSION	CHRONIC
303350	REACTION DEPRESSIVE AFFECTIVE
303351 DEPRESSION	ACUTE
303353 ENDOGENOUS	DEPRESSION
303354 RECURRENT	DEPRESSION

303372 ANXIET	Y DEPRESSION
303389 DEPRESSION	
303390 OBSERVED	DEPRESSION
303394 EXOGENOUS	DEPRESSION
303395 REACTIVE	DEPRESSION
306197 CHRONIC	AGITATED DEPRESSION
309920 [X]Mild	depression

Appendix 2 – Suicide Assessment

The suicide outcomes were defined using the GPRD Read suicide codelist (attached) and either:

- a) The exposure blinded freetext¹ review carried out by 2 staff from TGRD (Europe) (Suicide broad), or
- b) The exposure blinded freetext review carried out by 2 staff from GPRD (Suicide narrow)

For the blinded text review, the GPRD free text was searched for instances of the following terms for patients who had a date of death recorded in GPRD:

- **"*suic*"**
- **"*self" "and "harm" in the same sentence**
- **"*overdos*"**
- **"*over-dos*"**
- **"*harmful*" and "*thought*" in the same sentence**

In an attempt to reduce any misclassification of suicide outcomes, only freetext pertaining to the last 4 events within 6 months of the death date for each patient was scrutinised (i.e. text for those events closest to the death record).

Furthermore, when one of these terms appeared in the free text, only the text within 25 words of either side of the search term was extracted.

For the narrow review of the freetext, strict criteria were used for considering a suicide outcome, such that

- It was only considered a suicide event if the freetext record appeared to be reporting the actual suicide itself, for example "suicide on railway", "found hanging..." etc. and occurred within 6 months of the death date
- Text pre- and post-suicide event was reviewed to verify this where relevant and where text were available
- freetext which was considered to be related to fatal overdoses was considered as a suicide event where the text was close to death date and the text suggested it was

¹ GPRD freetext: Much of the data entered into practice management systems by the GP is in structured fields and uses either a medical or product dictionary. This is easily searchable and is used for most GPRD research. The GP is also able to enter information in an unstructured "free text" field. This provides vital additional information in the case of the suicide outcome. An example of free text is provided below:

"WEEPY && SPIRITS LOW 2 - 3/52 ~~~~~ IN HOSPITAL 2/7 SLEEP OK NO **SUICIDAL** THOUGHTS (FATHER COMMITTED **SUICIDE**) DISCUSSED RESTARING ANTI - DEPRESSANTS"

intentional (for these patients other free text events were also considered to understand whether this was a fair assumption or not.

For the ***broad*** review of the freetext more lenient criteria were used for considering a suicide outcome, such that

- It was considered a possible suicide if the free-text appeared to be reporting suicidal intent or the suicide itself, and the date of death was within 6 months of the free text

Appendix 3 - GPRD study summary



Excellence in Public Health Research

The Risk of Depression and Suicidal Behaviour among Patients Treated with Gonadotropin Releasing Hormone (GnRH) Agonists

Summary of Results

06 December 2010

Prepared by [REDACTED] GPRD, UK

This study was approved by ISAC (Protocol number 10_030)

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INTRODUCTION

Gonadotropin-releasing hormone (GnRH) agonists (goserelin, leuprorelin, triptorelin, buserelin, nafarelin) are mainly prescribed to treat uterine fibroids and endometriosis in women, and prostate cancer in men. These conditions, especially endometriosis and prostate cancer, are often severe resulting in pain and discomfort and may itself lead to depression or suicide.

This study was carried out to assess the association between the use of GnRH agonists and depression and suicidal outcomes, and to put these results in context of any association which may exist due to the underlying condition itself.

The objectives of the study were as follows:

1. To describe the prescribing and drug-utilization of GnRH agonists in the GPRD
2. To estimate the incidence rates of depression and suicidal behaviour in patients using GnRH agonists stratified by indication for treatment and exposure characteristics
3. To estimate the incidence rates of depression and suicidal behaviour in patients with the indication for treatment but untreated with GnRH agonists in GPRD
4. To estimate the relative risk of depression and suicidal behaviour in users of GnRH agonists.
5. To identify the risk factors associated with the development of depression and suicidal behaviour in patients with endometriosis prescribed GnRH agonists.

STUDY POPULATION

The following study populations were included:

1. Patients prescribed GnRH for the first time in GPRD for any indication
2. Control patients matched by age, sex, calendar year and practice
3. Patients with an indication for GnRH treatment (such as endometriosis, uterine fibroids or prostate cancer), but are not exposed to GnRH treatment and have no history of use
4. Control patients matched by age, sex, calendar year and practice

STUDY DESIGN

Unexposed patients

The characteristics of unexposed patients with the underlying disease (population 3) and their matched controls were described at baseline. Time with current or recent exposure to GnRH was excluded and analyses were stratified by type of indication for GnRH treatment.

Exposed patients

The characteristics of patients receiving GnRH agonists (population 1) and their matched controls were described at baseline. For exposed patients, the characteristics were also described at a random prescription date post-initiation by indication and GnRH drug type.

Outcomes

1. Suicidal ideation was identified in GPRD using the relevant Read codes
2. Suicide as cause of death was identified by examining death certificates
3. Suicide outcomes were identified in GPRD using the relevant Read codes or by examining the free-text using the following two approaches:
 - a. Narrow definition –an event was considered a suicide if the free-text term explicitly identified the occurrence of a suicide
 - b. Broad definition –an event was considered a suicide if the free-text term was broadly suggestive of a suicide or a suicide attempt
4. Incident depression was identified in GPRD with Read codes or prescriptions for antidepressants. Two lists of Read codes were used:
 - a. Narrow definition – where codes for bipolar and manic depression are excluded
 - b. Broad definition – where codes for bipolar and manic depression are included
5. Admission to hospital due to depression (recorded in HES)

Analyses

Cohort analysis

A Cox regression model was used to evaluate the associations between the risk of the various outcomes and indication for GnRH treatment in the study population of unexposed patients with an indication for treatment and their matched controls. A Poisson regression model was used to evaluate the associations between the risk of the various outcomes and GnRH treatment stage for the study population of patients exposed to GnRH and their matched controls. Risks were estimated relative to the unexposed control population and the population of past GnRH users.

Nested-case control analysis

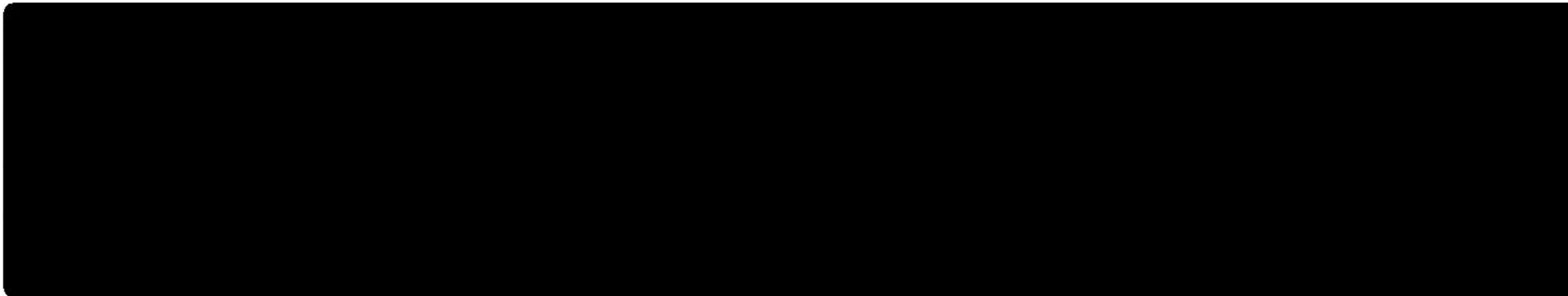
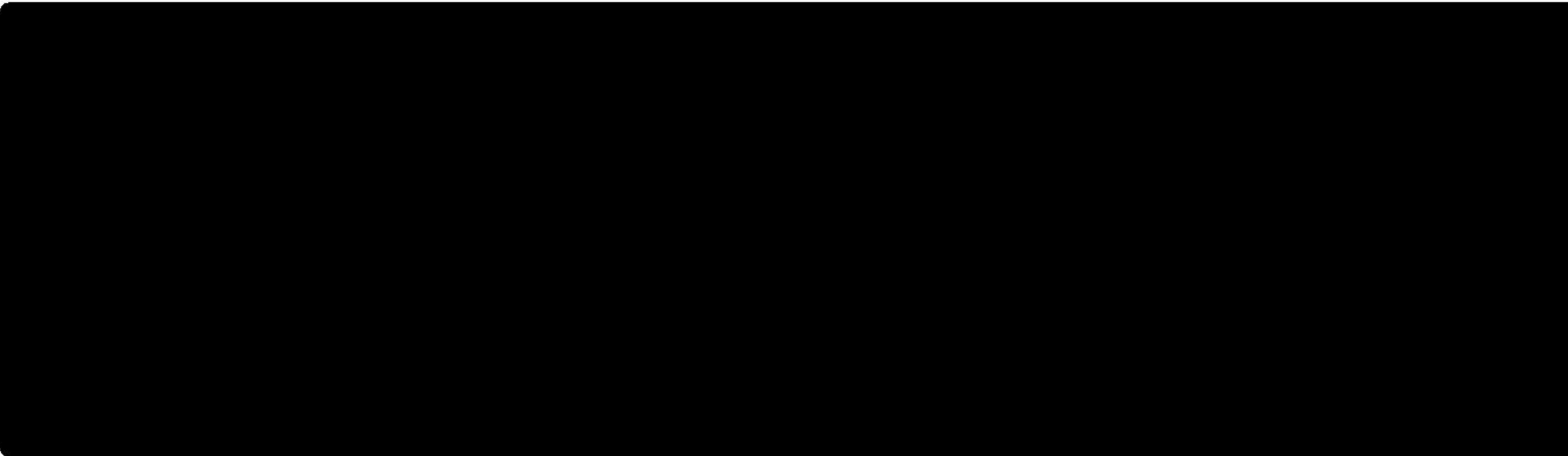
A nested case-control analysis within the cohort of exposed patients was carried out to further assess the association between treatment and outcome. Using the study time as defined for this population in the cohort analyses, cases of each outcome were identified. The risk sets corresponding to these cases were identified and up to 4 controls were selected from these sets matched by year of birth, gender and indication.¹

¹ Note that under this risk-set sampling approach, a future case was permitted to be a control for a prior case and a subject was allowed to be selected as a control subject more than one.

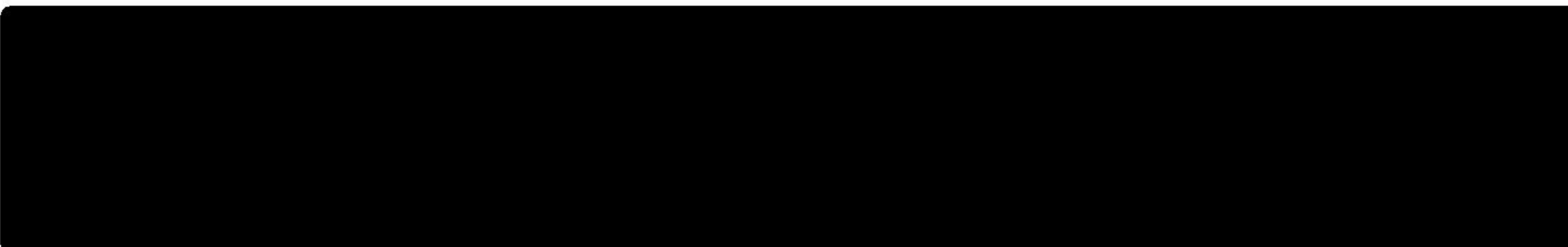
KEY FINDINGS

Baseline characteristics

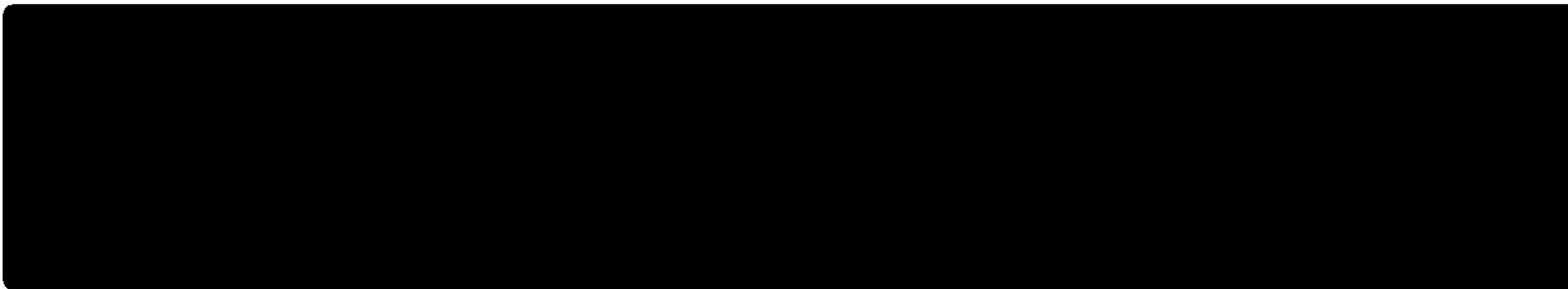
Exposed patients



Unexposed patients with an indication for treatment



² Note that classification of the indication for treatment here was based on a list of specific codes and not on a broad code list



Exposure characteristics

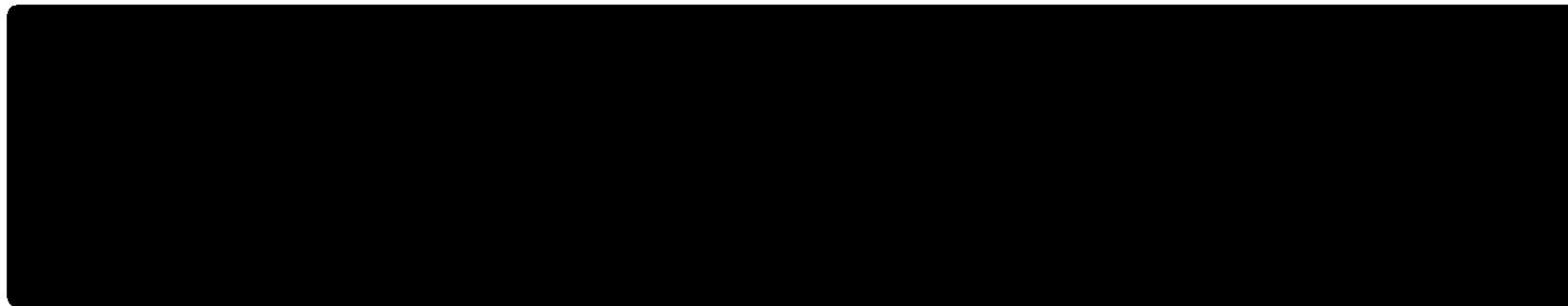


Table 1
Exposure
characteristics
by indication

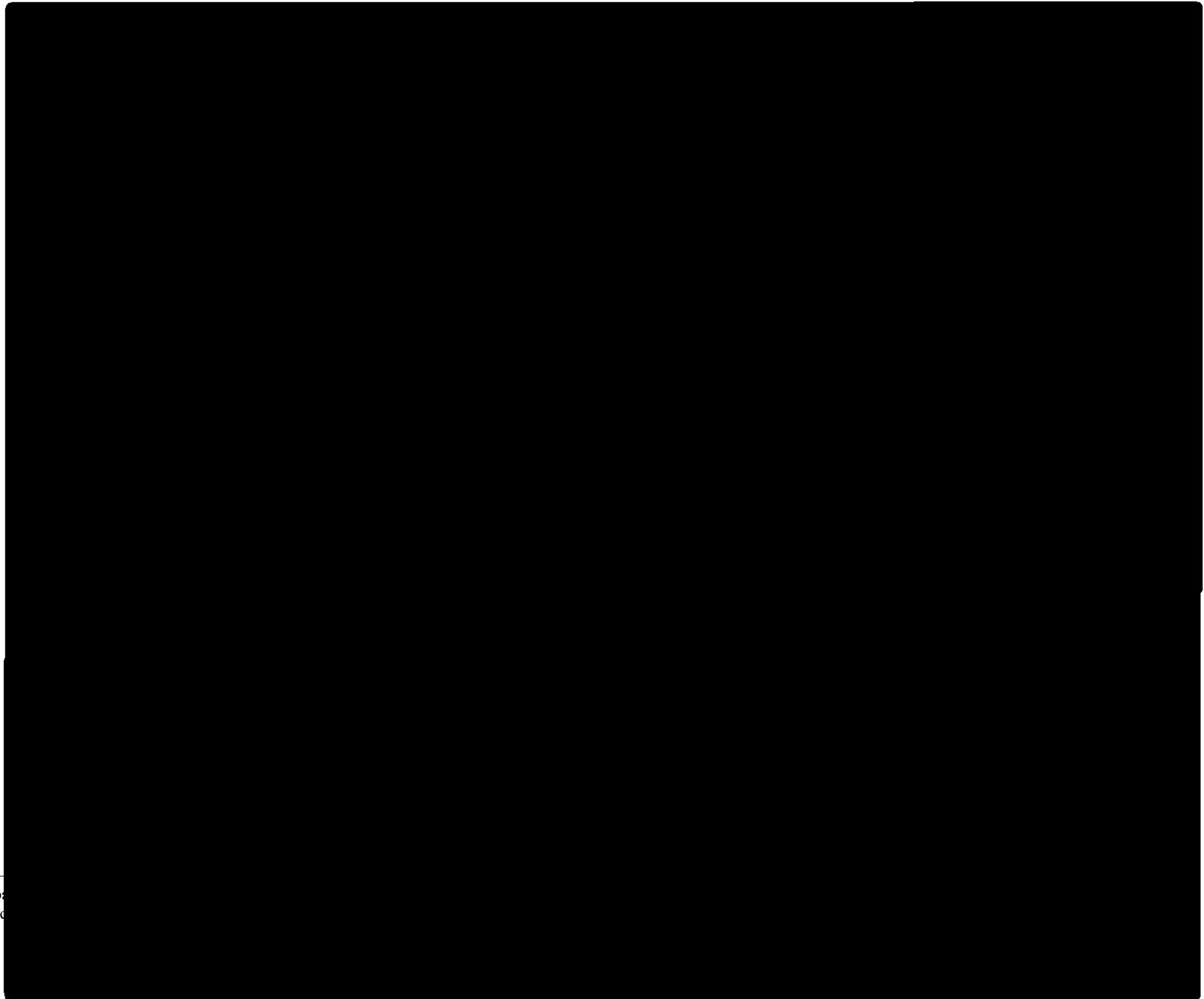
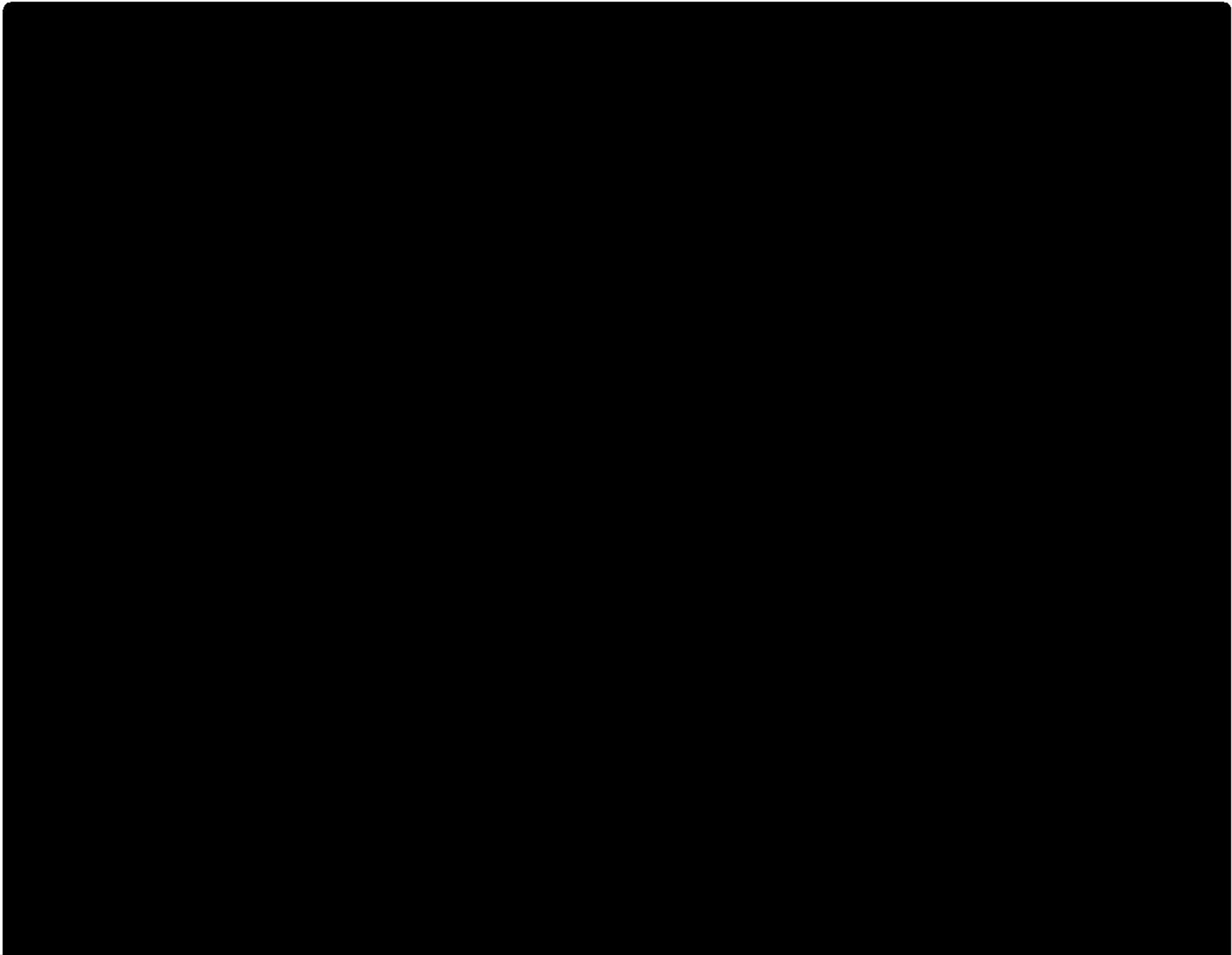
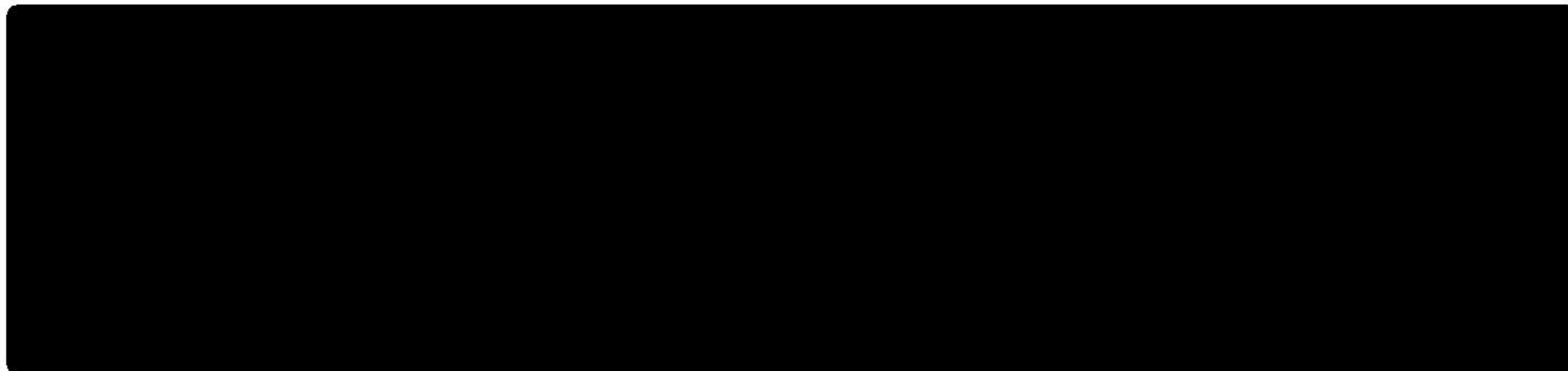
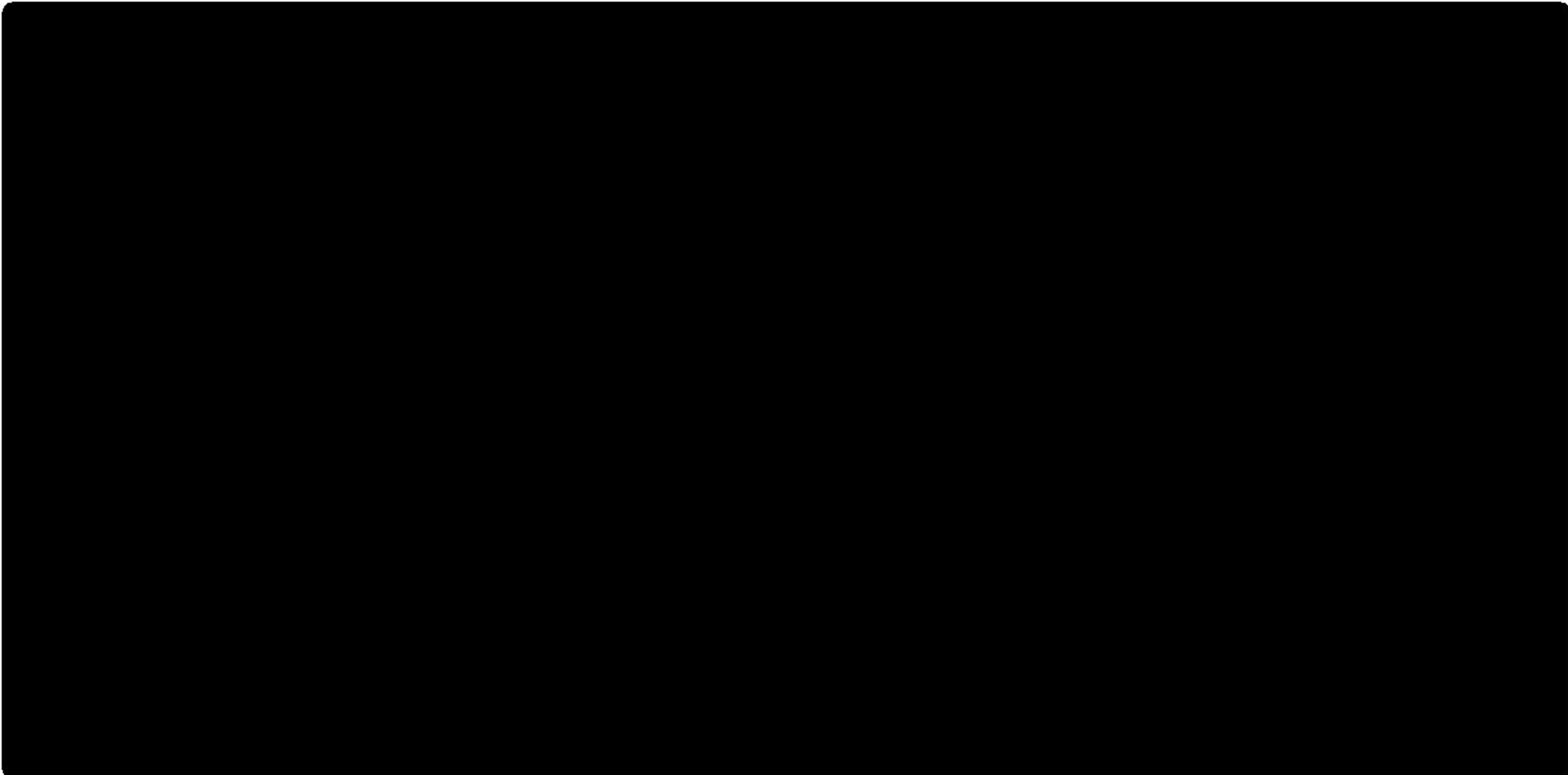


Table 2

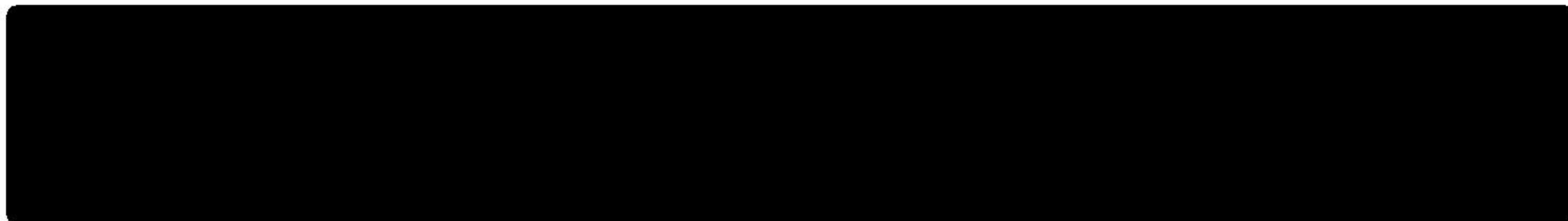
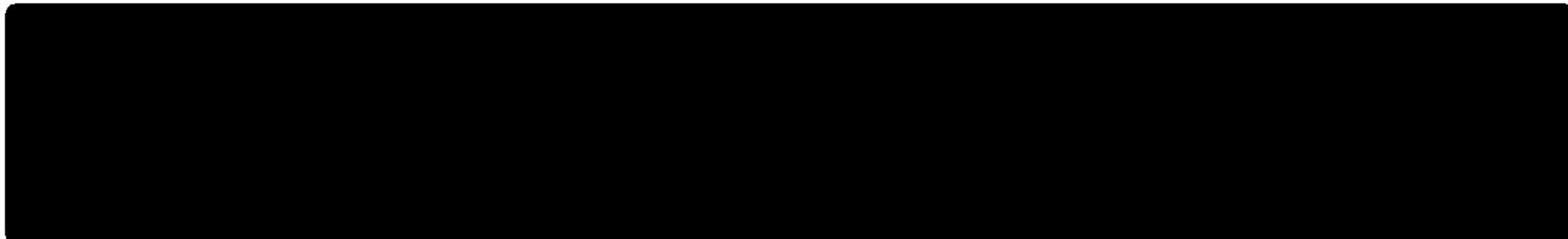
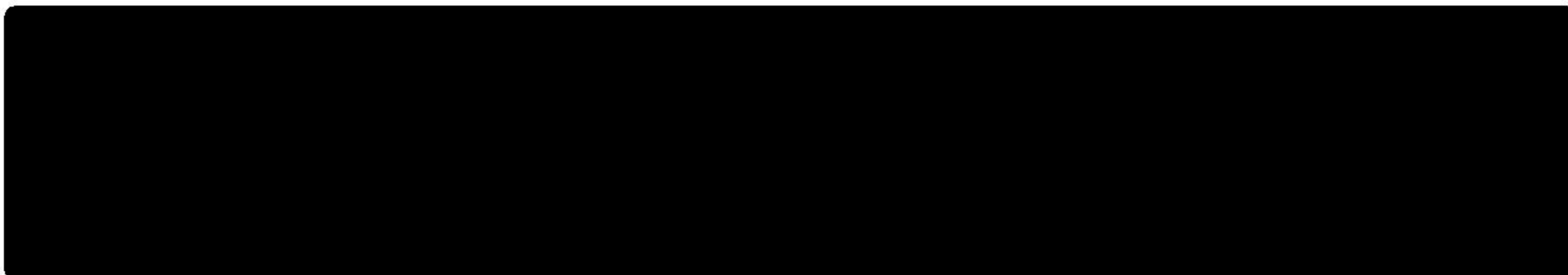
**Exposure
characteristics**

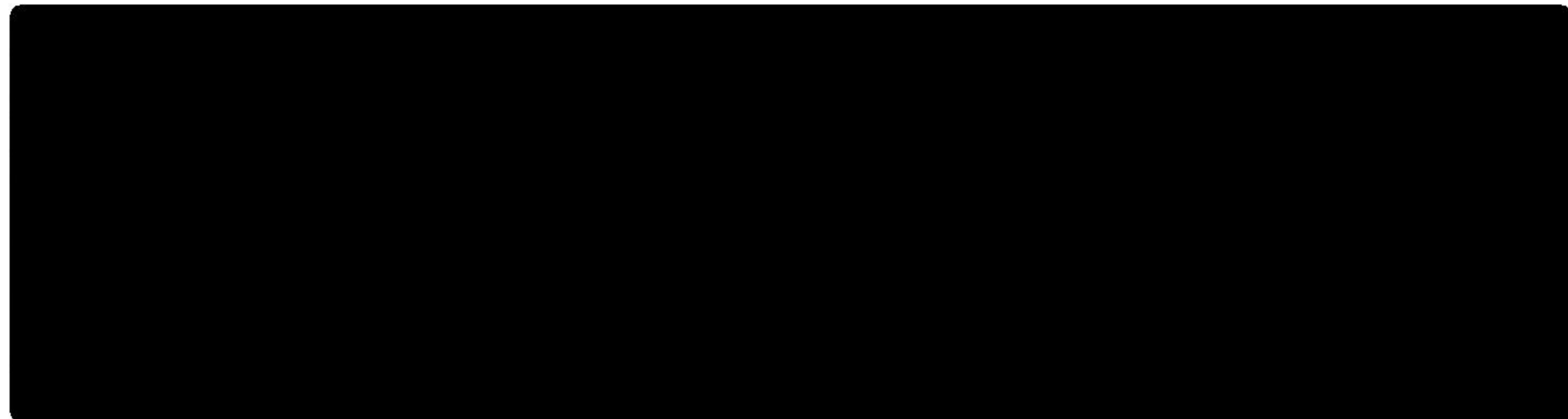
by GnRH type





Relative risk of outcomes





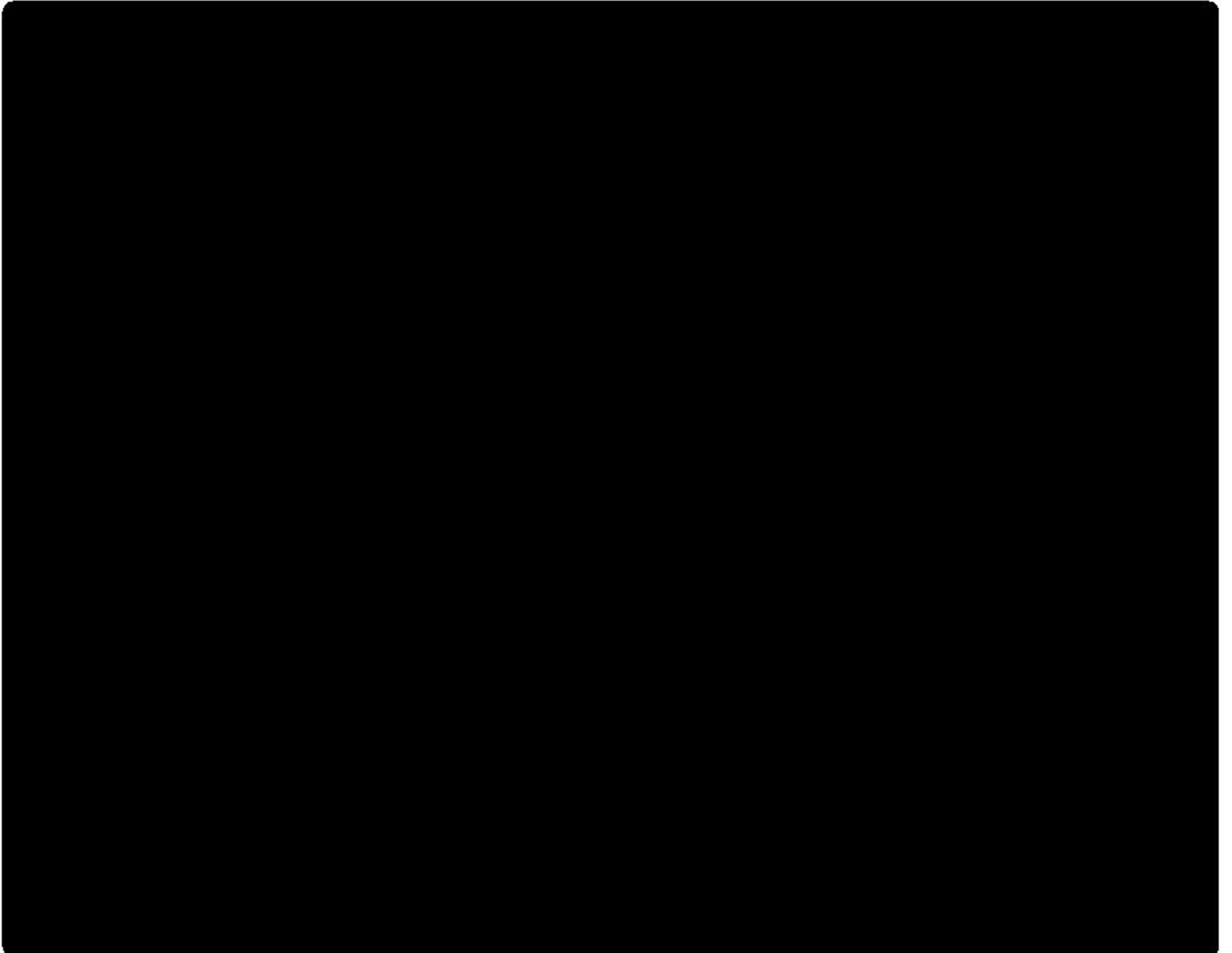


Figure 1.1 Relative risks of suicide and incident depression among patients with endometriosis (where a relative risk estimate could not be estimated due to insufficient numbers, a point estimate of 1.0 without a 95% confidence interval (95%CI) is displayed instead).

[Redacted text]

[Redacted text]

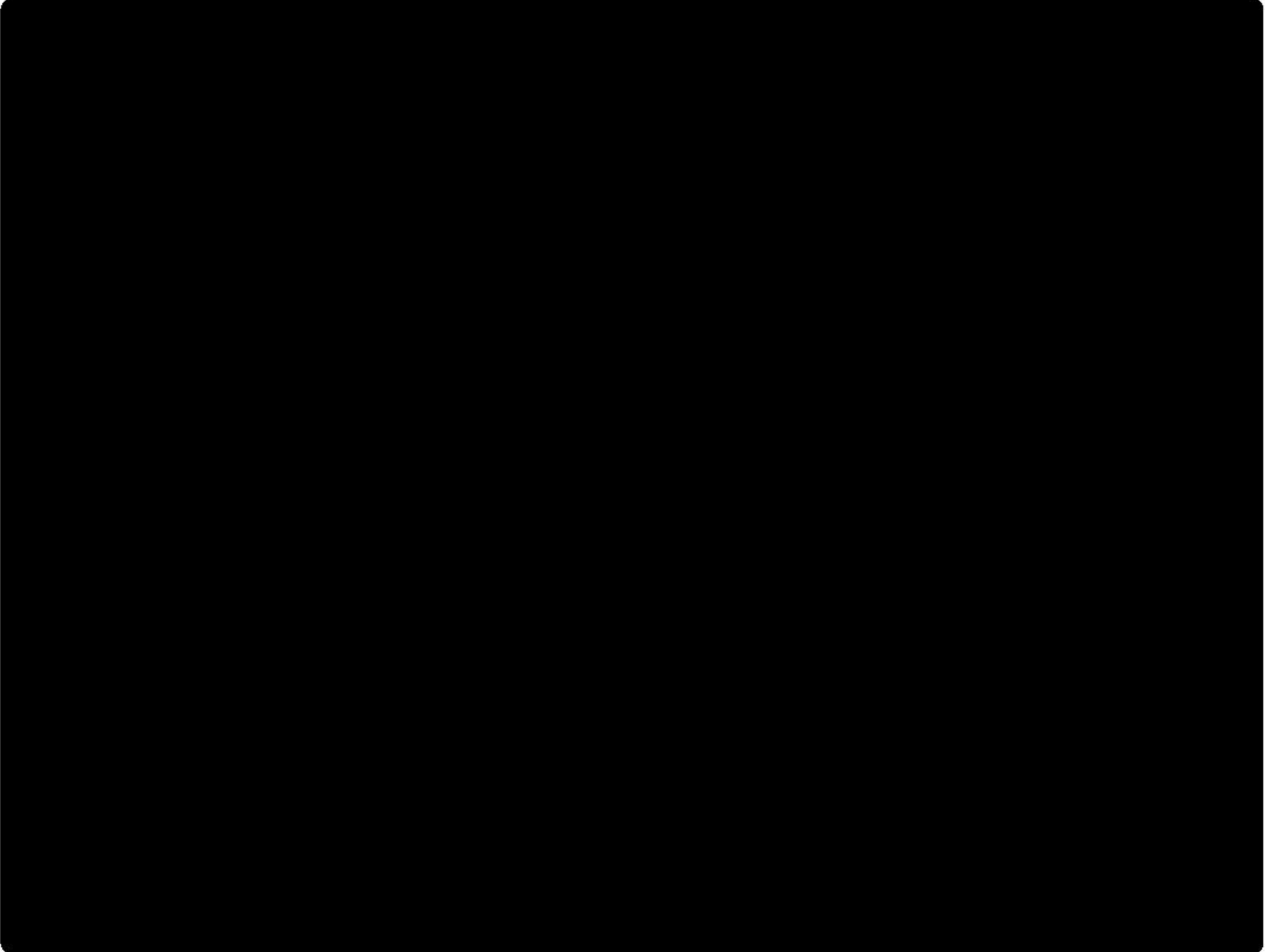
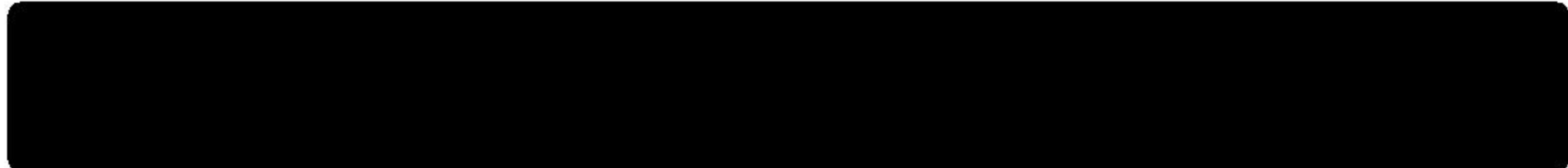


Figure 1.2 Relative risks of suicide and incident depression among patients with uterine fibroids



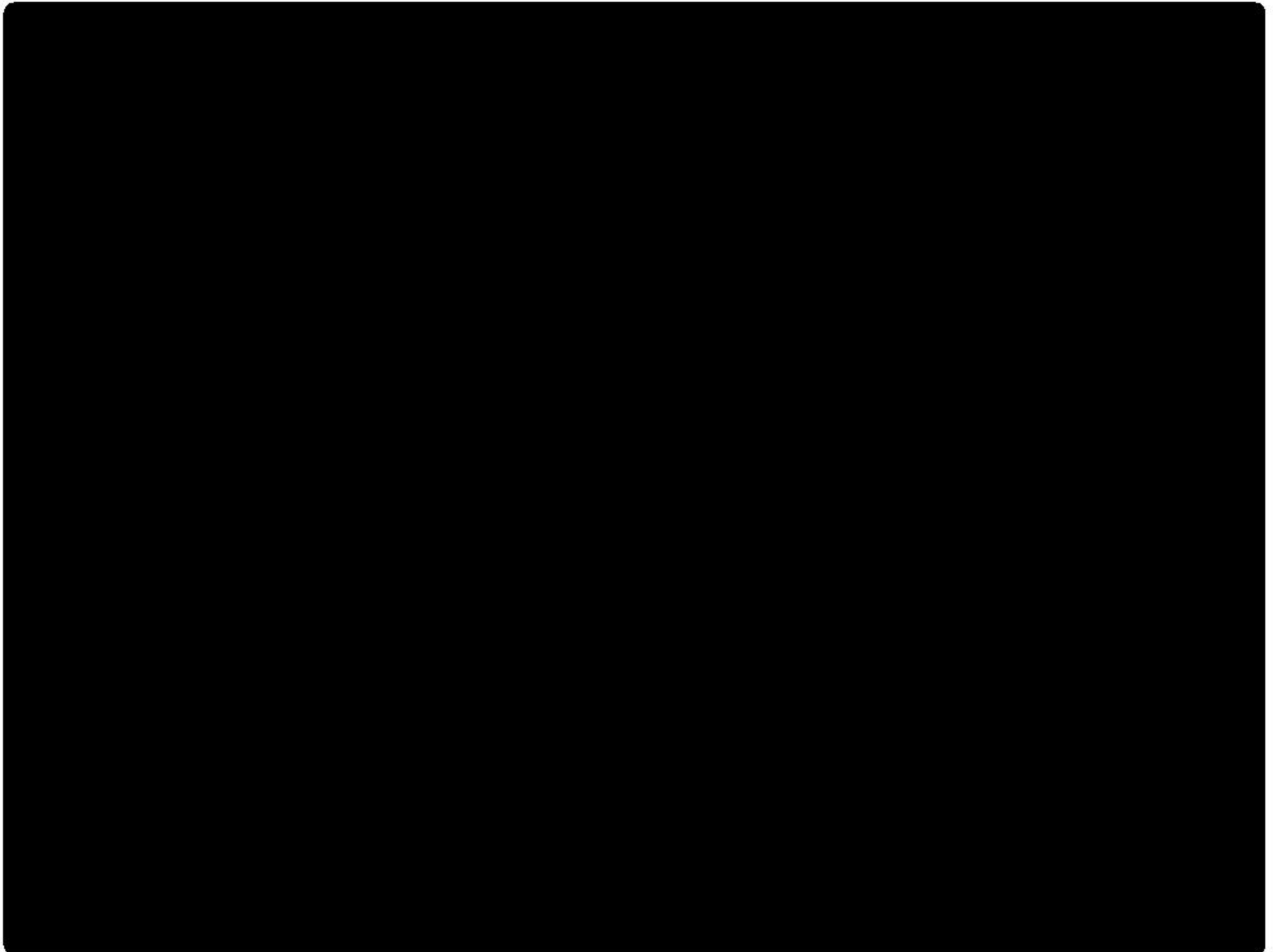
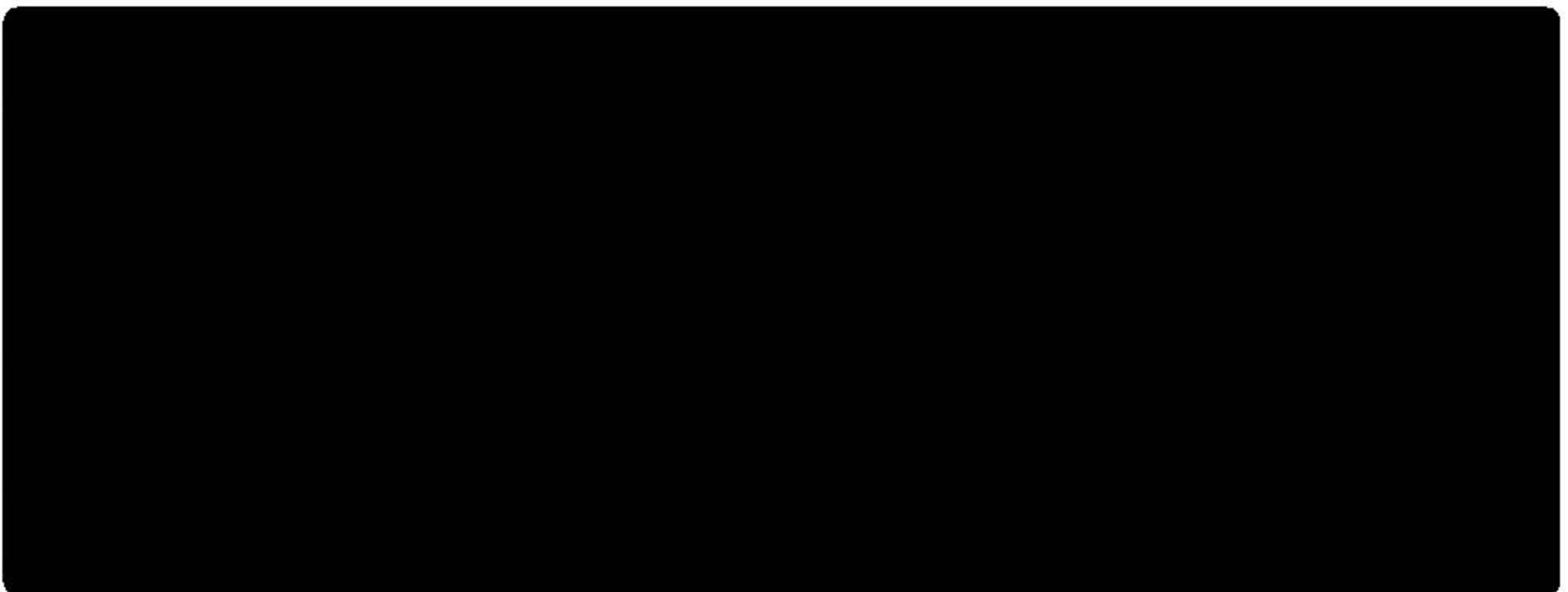
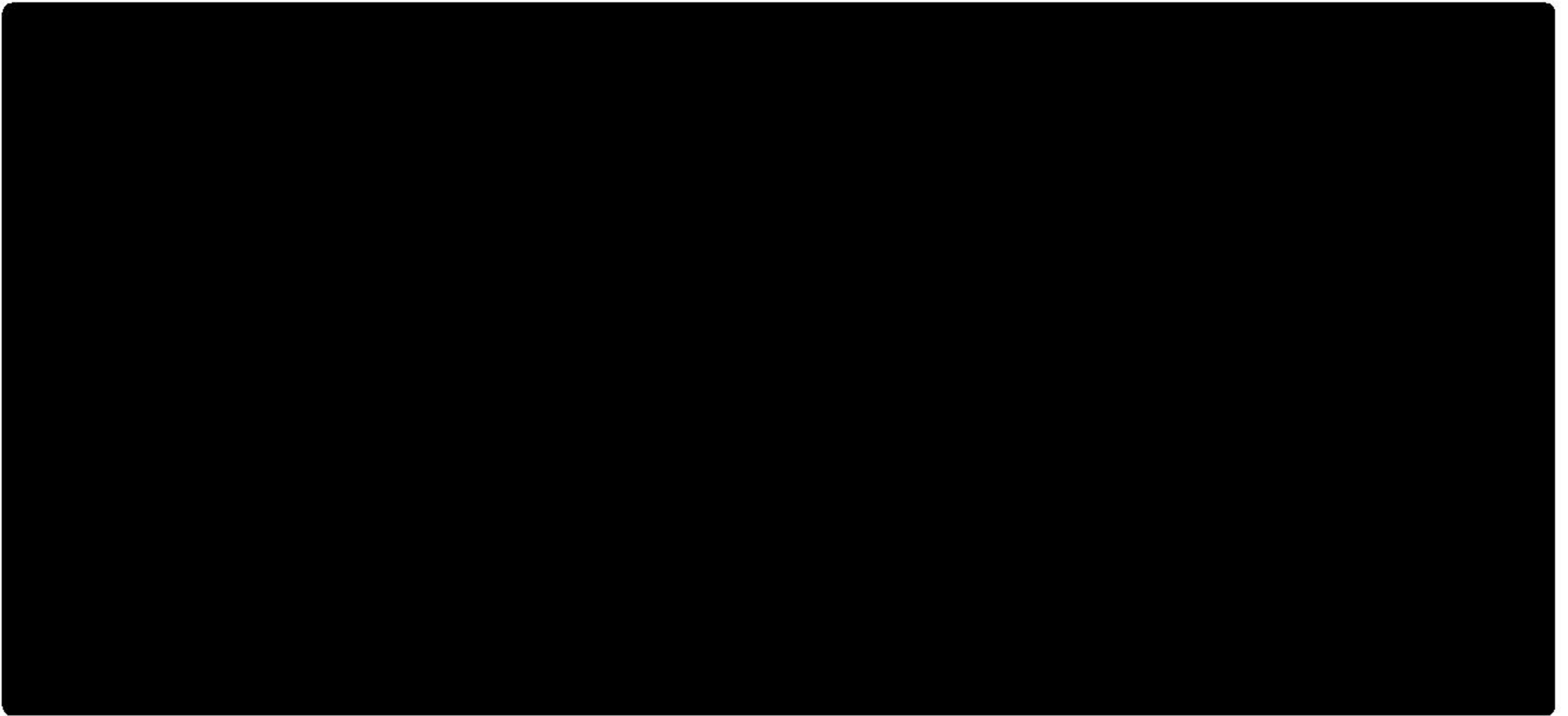


Figure 1.3. Relative risks of suicide and incident depression among patients with prostate cancer (where a relative risk estimate could not be estimated due to insufficient numbers, a point estimate of 1.0 without a 95% confidence interval (95%CI) is displayed instead).





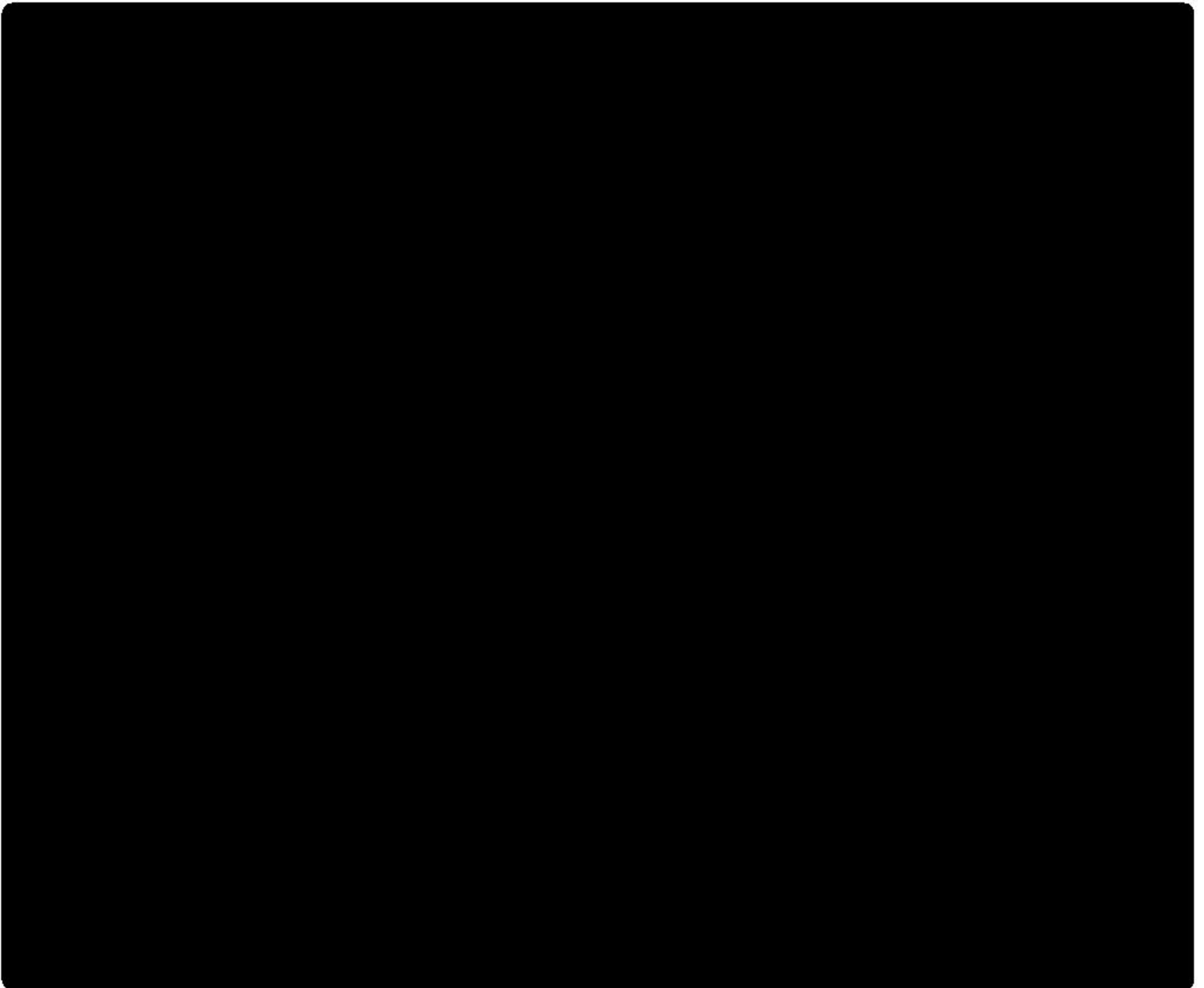
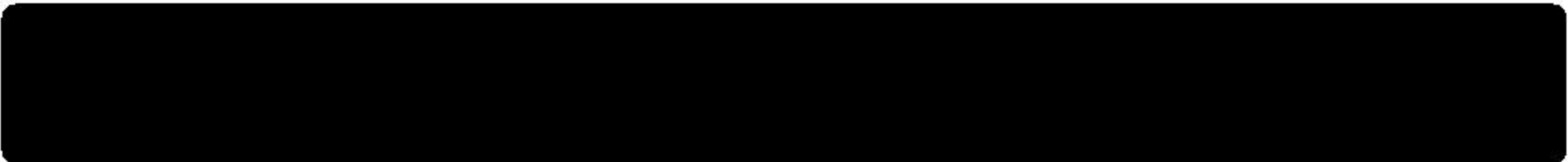


Figure 1.4 Relative risks of suicide and incident depression among patients with endometriosis (where a relative risk estimate could not be estimated due to insufficient numbers, a point estimate of 1.0 without a 95% confidence interval (95%CI) is displayed instead).



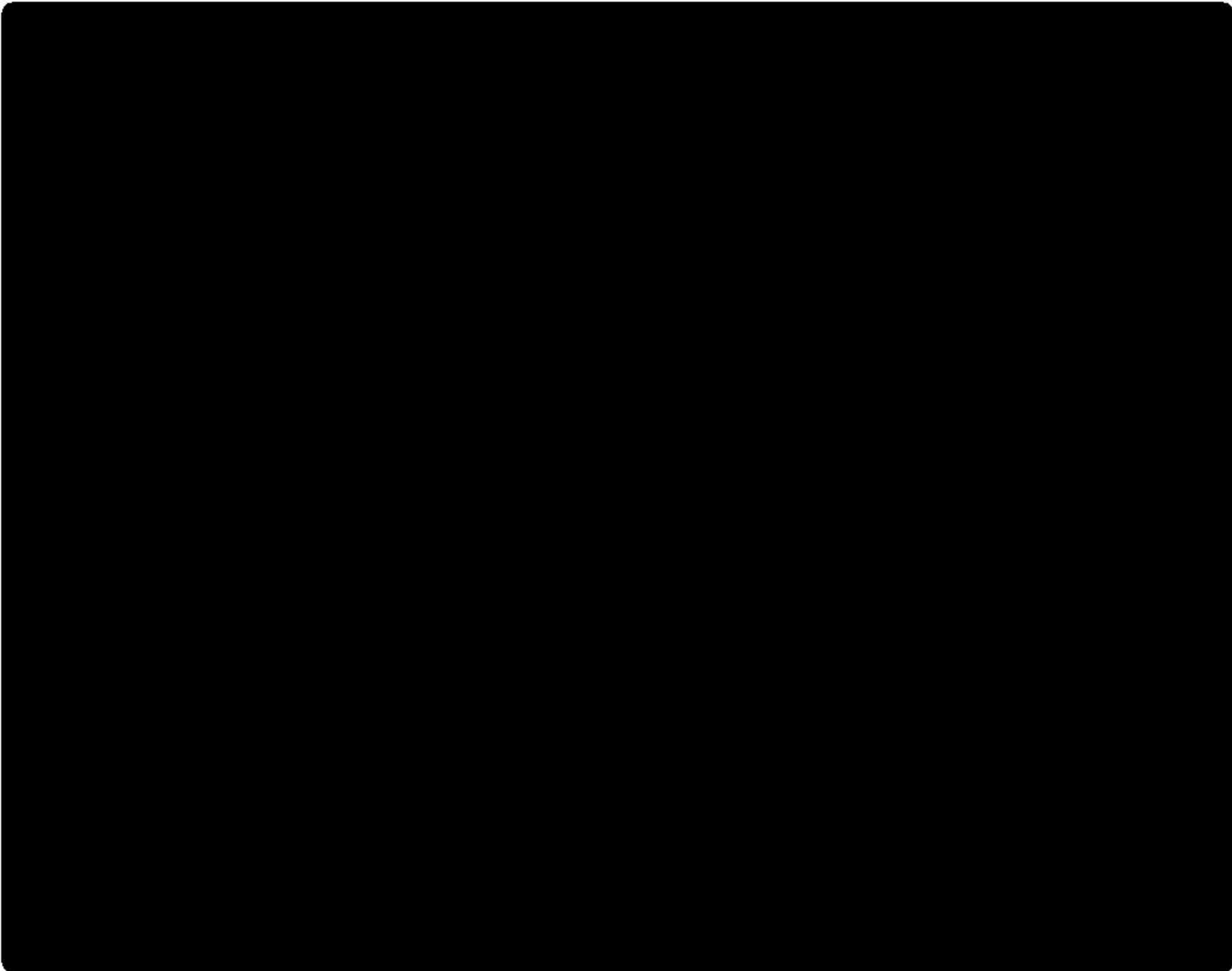


Figure 1.5 Relative risks of suicide and incident depression among patients with uterine fibroids (where a relative risk estimate could not be estimated due to insufficient numbers, a point estimate of 1.0 without a 95% confidence interval (95%CI) is displayed instead).



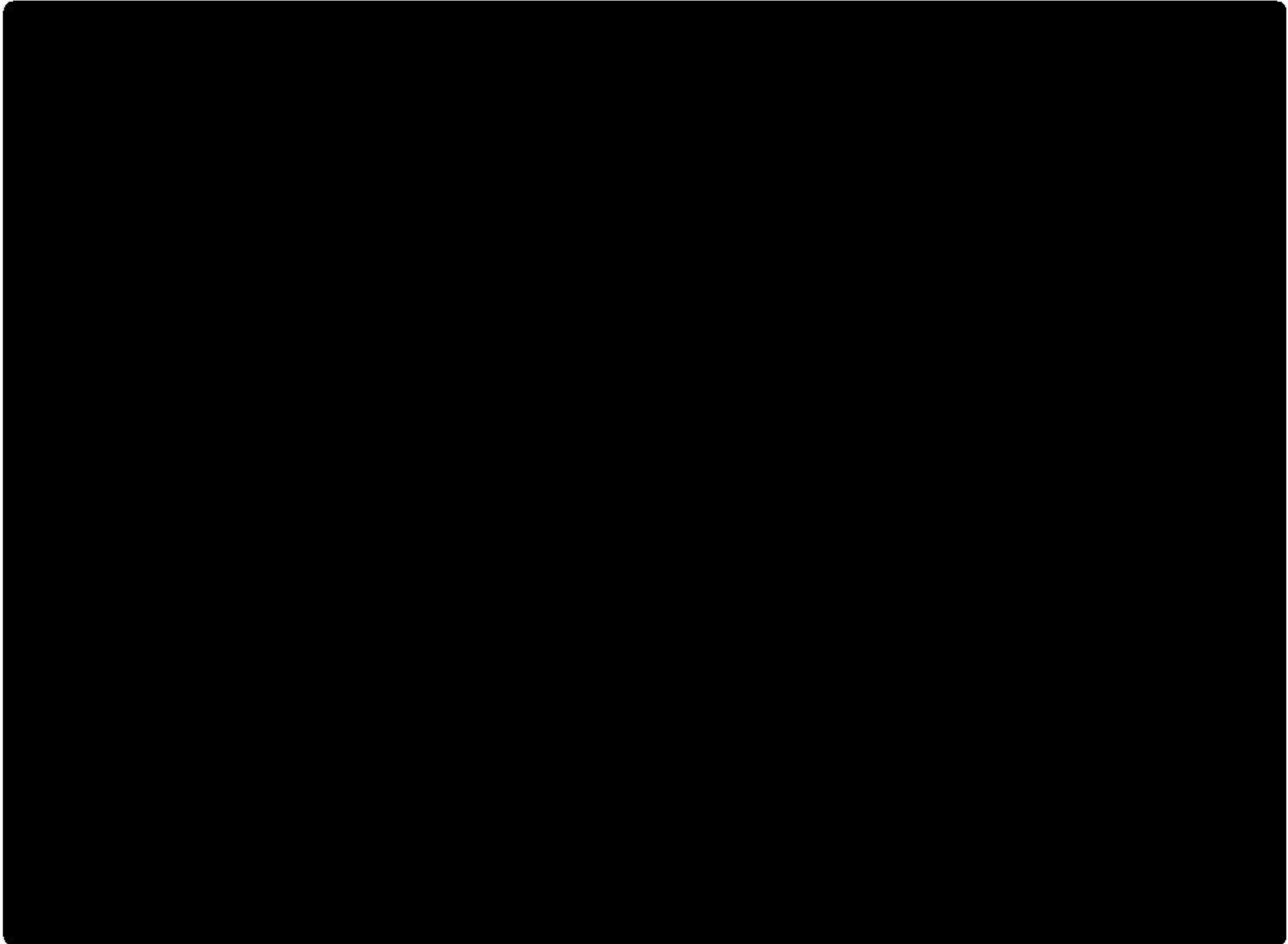


Figure 1.6 Relative risks of suicide and incident depression among patients with prostate cancer (where a relative risk estimate could not be estimated due to insufficient numbers, a point estimate of 1.0 without a 95% confidence interval (95%CI) is displayed instead).



Nested case-control

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CONCLUSIONS

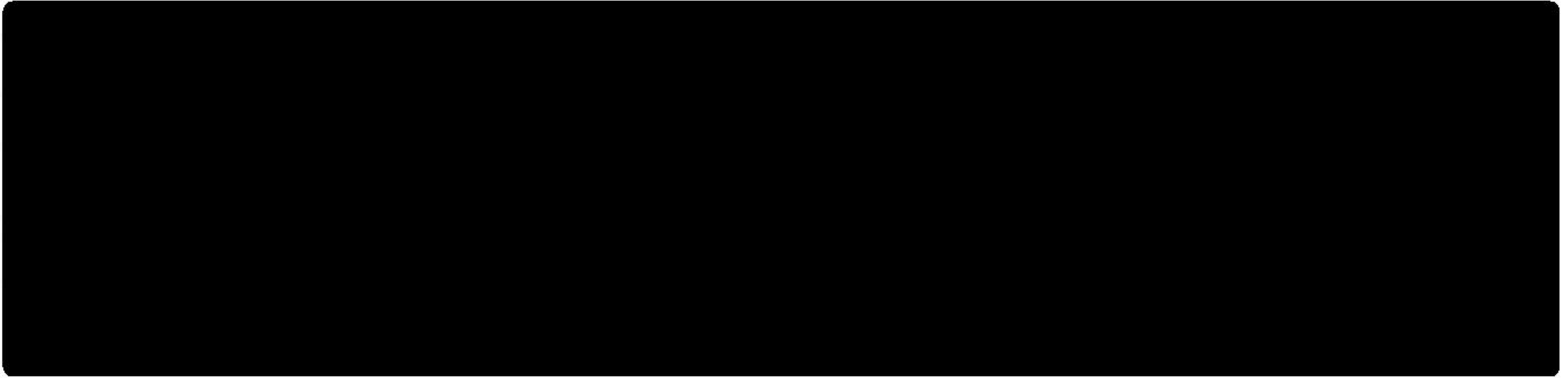
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

STUDY LIMITATIONS



Appendix 4 - GPRD study complete report



Excellence in Public Health Research

The Risk of Depression and Suicidal Behaviour among Patients Treated with Gonadotropin Releasing Hormone (GnRH) Agonists

Report

06 December 2010

Prepared by [REDACTED] GPRD, UK

This study was approved by ISAC (Protocol number 10_030)

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OBJECTIVE

1. To describe the prescribing and drug-utilization of GnRH agonists in the GPRD
2. To estimate the incidence rates of depression and suicidal behaviour in patients using GnRH agonists stratified by indication for treatment and exposure characteristics
3. To estimate the incidence rates of depression and suicidal behaviour in patients with the indication for treatment but untreated with GnRH agonists in GPRD
4. To estimate the relative risk of depression and suicidal behaviour in users of GnRH agonists.
5. To identify the risk factors associated with the development of depression and suicidal behaviour in patients with endometriosis prescribed GnRH agonists..

METHODS

The study specification was provided separately, containing full details on the code lists used, dated 12th August 2010.

Information for the study was obtained from the General Practice Research Database (GPRD), the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) Death certificates.

General Practice Research Database (GPRD)

The GPRD comprises the computerized medical records of general practitioners. General practitioners (GP) play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded in the GPRD include demographic information, prescription details, clinical records, preventive care provided, specialist referrals, hospital admissions and their major outcomes.

Hospital Episode Statistics (HES)

The Hospital Episode Statistics (HES) data contain details of all admissions to NHS hospitals in England. The patients include private patients and those resident outside of England, who were treated in NHS hospitals, as well as care delivered by treatment centres (including those in the independent sector) funded by the NHS. All NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts are included.

ONS Death certificates

The ONS Death certificate data contains the date and cause of death for England and Wales.

Study Design

The study design includes the use of both a cohort analysis and a nested-case control analysis.

Study Period

The study period was from 01/01/1989 to 30/06/2010.

Study Population

The following populations consisted of:

1. Patients prescribed GnRH for the first time in GPRD for any indication, and control patients matched by age, sex, calendar year and practice.
2. Patients with an indication for GnRH treatment (namely endometriosis, uterine fibroids or prostate cancer) but without a prescription for GnRH treatment, and control patients matched by age, sex, calendar year and practice.

Study population 1

The date of the first GnRH prescription during the study period was defined as the index date. Patients were identified using the following criteria:

All patients in GPRD (11,719,847):

- who are acceptable¹ (10,329,509)
- who have a prescription for GnRH (47,485)
- who are male or female (47,482)
- where their first record is during UTS follow-up (38,977)
- who are aged at least 18 at this date (38,787)
- who have at least 12 months of previous follow-up and at least one day of post-index follow-up (32,685)

Patients will be flagged by their first indication for treatment (endometriosis, uterine fibroids, prostate cancer, none) by examining records three years before initiation of GnRH agonists and up to 6 months after.

Exclusion criteria

Patients with a record of the following prior to or on index date:

- suicide attempts (32,332)
- alcoholism or drug abuse (31,534)
- severe mental illness (such as schizophrenia, bipolar disorder, dementia, personality disorder or schizoaffective disorder) (31,312)

Study population 2

Inclusion criteria

All patients in GPRD (11,719,847):

- who are acceptable (10,329,509)
- who are male or female (10,329,229)
- who have no record of endometriosis, uterine fibroids or prostate cancer (10,174,420)
- who have no record of a prescription for GnRH (10,158,859)
- who have at least 12 months of follow-up (7,589,841)

¹ This is defined by the GPRD group. Acceptable patients are required to have a valid gender, date of birth and registration details

- who are aged at least 18 at the start of follow-up (5,550,541)

Study population 1 will be matched to three patients from study population 2 by age, sex and practice.

Exclusion criteria (performed post-matching)

Patients with a record of the following prior to or on index date:

- suicide attempts,
- alcoholism or drug abuse,
- severe mental illness (such as schizophrenia, bipolar disorder, dementia, personality disorder or schizoaffective disorder)

Cohort: 31,310 exposed cases matched to 93,856

Study population 3

Inclusion criteria

All patients in GPRD (11,719,847):

- who are acceptable (10,329,509)
- who have a clinical or referral record for endometriosis, uterine fibroids or prostate cancer (154,812)
- who are male or female (154,809)
- who have a record on or after 01/01/2000 (87,108)
- who have a record during UTS follow-up1 (71,515)
- who are aged at least 18 at this date (71,444)
- who have at least 12 months of previous follow-up and at least one day of post-index follow-up (60,362)
- who have no record of a prescription for GnRH on or prior to index date (55,105)

Index date is defined as the first record of an indication during the study period, in patients with at least 12 months of previous follow-up.

Exclusion criteria

Patients with a record of the following prior to or on index date:

- suicide attempts (54,513)
- alcoholism or drug abuse (53,285)
- severe mental illness (such as schizophrenia, bipolar disorder, dementia, personality disorder or schizoaffective disorder) (52,862).

Study population 4

Inclusion criteria

All patients in GPRD (11,719,847):

- who are acceptable (10,329,509)
- who are male or female (10,329,229)
- who have no record of endometriosis, uterine fibroids or prostate cancer (10,174,420)
- who have no record of a prescription for GnRH (10,158,859)
- who are registered on or after 01/01/2000 (7,971,860)
- who have at least 12 months of follow-up (6,704,266)
- who are aged at least 18 at start of follow up (4,857,430)

Study population 3 will be matched to three patients from study population 4 by age, sex and practice.

Exclusion criteria (performed post-matching)

Study population 3 will be analysed for GnRH prescribing. Patients with prescribing prior to or on index date will be excluded (with their matches). Patients with prescribing after index date will be censored at this point.

Additionally, patients with a record of the following prior to or on index date:

- suicide attempts,
- alcoholism or drug abuse,
- severe mental illness (such as schizophrenia, bipolar disorder, dementia, personality disorder or schizoaffective disorder)

Cohort: 52,862 cases with indication matched to 158,506 controls

For analyses where the outcome event was defined using hospitalisation data or cause of death data, patients were additionally restricted to those where their index date was during the HES follow-up period² and the ONS follow-up period³.

Descriptive data on the cohort

Baseline characteristics

Descriptive data on the study population 1 and 2, and for study populations 3 and 4 were examined. Gender and year of treatment initiation/diagnosis were described. Length of follow-up (years), age, BMI, smoking Status and drinking Status were examined at index date. Socioeconomic status was examined at the practice and patient (small area) level. History of Diabetes Mellitus, cerebrovascular disease, ischaemic heart disease, congestive heart failure, peripheral vascular disease, hypertension, Parkinson's disease, restless legs syndrome, fibromyalgia, COPD, asthma, urinary problems and gastrointestinal problems were examined by looking for records prior to the index date. Treatment with oral corticosteroids, benzodiazepine, NSAIDs or Cox-2 inhibitors, analgesic opioids, hormonal therapeutics, oral contraceptives and aromatase inhibitors were examined by investigating prescribing in the 90 days prior to index date.

For study population 1, this table will also include the indication for treatment and the number of patients who initiate GnRH monotherapy versus additional hormonal therapeutics.

Current exposure characteristics

This analysis will describe the current exposure characteristics of GnRH medication and evaluate how GnRH medications are used in actual clinical practice in the UK. A random prescription was chosen for each patient in study population 1 and used as the index date. Descriptive data on the cohort as of this date was examined for study population 1 overall,

² The period of data collection for the HES (01 April 1997 to 30 September 2009)

³ The period of data collection for the ONS death certificates (01 January 2001 to 30 September 2009)

and repeated for each indication, and for each GnRH substance (Buserelin, Goserelin, Leuprorelin, Nafarelin, Triptorelin).

Evaluation of exposure misclassification

In order to determine the extent of this misclassification bias, the GPRD free-text of population 2 was searched for the mention of GnRH prescribing (goserelin, leuprorelin, triptorelin, buserelin, nafarelin or their trade names – see Appendix III for details) for those practices with above average recording of free-text. The percentage of patients from these practices with GnRH prescribing in the free-text was recorded.

Exposure classification and outcomes

Exposures

Patients will be followed from the index date until censoring (the earliest of the occurrence of the outcome of interest, they leave the practice, they die, or the end of data collection). The follow-up period for population 1 was classified according to treatment and categorised into periods of:

- Current treatment: the period when there is a valid prescription until the expected end of use (a 1M agent will be assumed to last for 40 days; a 3M agent will be assumed to last for 118 days). Patients will be assumed to be continually exposed unless a gap of more than 10 days from the end of current use occurs.
- Recent treatment: the period between the expected end of use of a treatment until 30 days later.
- Past treatment: any subsequent follow-up time after recent treatment (until censoring or a further prescription).

Daily dosage and expected exposure periods

Daily dosage information for GnRH agonists was rarely recorded in the database for this population, and therefore the daily dosage has not been reported here. Instead the expected exposures for each treatment (i.e. for each Multilex product code) were

described as laid out in the summary of product characteristics (SPC) for that product. Where the expected treatment period was either missing, not clearly described in the SPC or left to the discretion of the clinician, the median length of treatment for that product based on prescriptions for the exposed cohort was used as the expected treatment length instead for analyses and described in tables as “unknown” or “as prescribed”. In the descriptive tables, GnRH prescriptions are therefore described as follows:

- 7 days
- 1 month
- 3 months
- As prescribed
- Unknown

Outcomes

1. Suicidal ideation was identified in GPRD using the relevant Read codes
2. Suicide as cause of death was identified by examining death certificates data
3. Suicide outcomes were identified in GPRD using the relevant Read codes *or* by examining the free-text in two separate approaches:
 - a. Narrow definition – a suicide outcome was recorded if the free-text term explicitly identified that a suicide had occurred
 - b. Broad definition – a suicide outcome was recorded if the free-text term was broadly suggestive of a suicide or a suicide attempt
4. Incident depression was identified in GPRD with Read codes or prescriptions for antidepressants. Two lists of Read codes were used:
 - a. Narrow definition – where codes for bipolar and manic depression are excluded
 - b. Broad definition – where codes for bipolar and manic depression are included
5. Admission to hospital due to depression (recorded in HES)

Patients with a history of depression or prescription for antidepressants at any time before the index date (i.e. first prescription of GnRH) were excluded from the analysis of incident depression in GPRD.

Appendix III references the Read codes, free text terms used to identify suicide cases and ICD codes. Free text was analysed by investigating the text associated with clinical records for patients identified as having died. Records between their index date and their end of follow-up were considered, and those within ± 6 months of death were examined. Two blinded reviews of the free-text were carried out. This resulted in two definitions of suicide outcomes which are described in this document as 1a and 1b above.

Patients were followed from the index date until the earliest of the outcome of interest, transfer out of the practice, last data collection⁴, or death. For each outcome, the incident record of the event occurring after index date was identified. The total period of follow-up was identified and recorded.

⁴ The earliest of the last data collection from the practice, the end of data collection from the HES, or the end of data collection from the ONS death certificates

Covariates

The following risk factors were investigated as potential confounders:

1. Small-area socioeconomic class
2. Number of GP visits (for any reason) in the 6 to 12 months before
3. Recent prescribing of NSAIDs, Cox-2 inhibitors, opioid analgesics, hormonal therapeutics
4. History of co-morbidities: Fibromyalgia[†], urinary problems (kidney disease, prostate problems), gastrointestinal problems (e.g. IBS, ulcers), menopause[†]
5. History of depression[‡]
6. Infertility
7. Duration of indication for treatment[¥]
8. Alcohol use

Age, calculated at the beginning of each window period (i.e. as a time-dependent variable where appropriate), was included in all models shown here.

Please note that for certain analyses (outcomes), if the number of events for a given covariate were too low overall or too low among the controls only, the covariate was not considered further.

[†] - only used where population includes indication of uterine fibroids or endometriosis

[‡] - only used in suicide cause of death and hospitalised depression analysis

[¥] - As this variable will be missing for all controls, its consideration in models which include "healthy controls" is likely to introduce problems of collinearity to the model and thereby affect inferences on the parameter estimates for the treatment covariate. Therefore, this covariate was only included in the nested case control analysis.

RESULTS OVERVIEW

Part I: Characteristics of the study population

1. Descriptive data on the cohort

Table 1.1 describes the population of patients who were exposed to GnRH agonists and the population of matched controls.

Table 1.2 describes the population of patients who had indication for treatment with GnRH agonists but who were unexposed, and the population of matched controls.

2. Exposure characteristics

Table 2.x describes the overall population of patients who were exposed to GnRH agonists, at a random prescription date for x, where x is:

- 1) all patients exposed
- 2) patients with indication of endometriosis
- 3) patients with indication of uterine fibroids
- 4) patients with indication of prostate cancer
- 5) patients with an unknown indication
- 6) patients receiving a prescription for Buserelin
- 7) patients receiving a prescription for Goserelin
- 8) patients receiving a prescription for Leuprorelin
- 9) patients receiving a prescription for Nafarelin
- 10) patients receiving a prescription for Triptorelin

Part II: Evaluation of potential biases in evaluating drug effects

3. Confounding by underlying disease severity

Table 3.x describes the incidence and the crude and unadjusted relative hazards for each outcome for patients with indication x compared to the matched controls, where x is:

- 1) endometriosis
- 2) uterine fibroids, and
- 3) prostate cancer.

4. Confounding by past exposure characteristics

Table 4.x describes the incidence and crude and unadjusted relative risks by past exposure characteristics for x compared to no use, where x is:

- 1) Hospitalised depression among patients with an indication of endometriosis
- 2) Suicide as cause of death among patients with an indication of endometriosis
- 3) Suicide outcome (broad) as defined in GPRD medical codes and free text among patients with an indication of endometriosis
- 4) Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an indication of endometriosis
- 5) Suicidal ideation among patients with an indication of endometriosis
- 6) Incident depression (broad) among patients with an indication of endometriosis
- 7) Relative rates of outcomes with GnRH exposure: Incident depression (narrow) among patients with an indication of endometriosis
- 8) Hospitalised depression among patients with an indication of uterine fibroids
- 9) Suicide as cause of death among patients with an indication of uterine fibroids
- 10) Suicide outcome (broad) as defined in GPRD medical codes and free text among patients with an indication of uterine fibroids

- 11)Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an indication of uterine fibroids
- 12)Suicidal ideation among patients with an indication of uterine fibroids
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- 18)Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an indication of prostate cancer
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- 23)Suicide as cause of death among patients with an unknown indication
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Part III: Relative rates of outcomes with GnRH exposure**5. Relative rates of outcomes during current GnRH exposure**

Table 5.x describes the crude and unadjusted relative risks for current and past GnRH exposure for x compared to no use and past use, where x is:

- 1) Hospitalised depression among patients with an indication of endometriosis
- 2) Suicide as cause of death among patients with an indication of endometriosis
- 3) Suicide outcome (broad) as defined in GPRD medical codes and free text among patients with an indication of endometriosis
- 4) Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an indication of endometriosis
- 5) Suicidal ideation among patients with an indication of endometriosis
- 6) Incident depression (broad) among patients with an indication of endometriosis
- 7) Relative rates of outcomes with GnRH exposure: Incident depression (narrow) among patients with an indication of endometriosis
- 8) Hospitalised depression among patients with an indication of uterine fibroids
- 9) Suicide as cause of death among patients with an indication of uterine fibroids
- 10) Suicide outcome (broad) as defined in GPRD medical codes and free text among patients with an indication of uterine fibroids
- 11) Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an indication of uterine fibroids
- 12) Suicidal ideation among patients with an indication of uterine fibroids
- 13) Incident depression (broad) among patients with an indication of uterine fibroids
- 14) Incident depression (narrow) among patients with an indication of uterine fibroids
- 15) Hospitalised depression among patients with an indication of prostate cancer
- 16) Suicide as cause of death among patients with an indication of prostate cancer
- 17) Suicide outcome (broad) as defined in GPRD medical codes and free text among patients with an indication of prostate cancer
- 18) Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an indication of prostate cancer
- 19) Suicidal ideation among patients with an indication of prostate cancer

- 20) Incident depression (broad) among patients with an indication of prostate cancer
- 21) Incident depression (narrow) among patients with an indication of prostate cancer
- 22) Hospitalised depression among patients with an unknown indication
- 23) Suicide as cause of death among patients with an unknown indication
- 24) Suicide outcome (broad) as defined in GPRD medical codes and free text among patients with an unknown indication
- 25) Suicide outcome (narrow) as defined in GPRD medical codes and free text among patients with an unknown indication
- 26) Suicidal ideation among patients with an unknown indication
- 27) Incident depression (broad) among patients with an unknown indication
- 28) Relative rates of outcomes with GnRH exposure: Incident depression (narrow) among patients with an unknown indication

6. Nested case-control study

For the population of exposed patients only, cases of each of the outcomes were identified and matched to up to four patients without the outcome from the same cohort by age, indication and index date. The number of cases for each outcome and the number of matched controls were as follows for each outcome:

- 1) Hospitalised depression:
 - a. 127 cases matched to 508 controls (1:4 matching)
- 2) Suicide outcome (broad) as defined in GPRD medical codes
 - a. 57 cases matched to 228 controls (1:4 matching)
- 3) Suicide outcome (narrow) as defined in GPRD medical codes
 - a. 13 cases matched to 52 controls (1:4 matching)
- 4) Suicidal ideation among patients
 - a. 58 cases matched to 232 controls (1:4 matching)
- 5) Incident depression (broad)
 - a. 4,452 cases matched to 17,759 controls (1:3.99 matching)
- 6) Incident depression (narrow)
 - a. 4,454 cases matched to 17,760 controls (1:3.99 matching)

Table 6.xa describes the characteristics of patients with an outcome of x compared to their controls and Table 6.xb describes the effects of current treatment use on outcome x compared to past use for each x, where x is each of the outcomes as described above.

Please note that a nested case-control analysis was not carried out for the outcome of suicide as cause of death as there were only 5 events recorded among the exposed population.

APPENDIX I: GLOSSARY OF TERMS

BMI	Body mass index
GnRH	Gonadotropin Releasing Hormone
GPRD	General Practice Research Database
HES	Hospital Episodes Statistics
IQR	Interquartile range
NHS	National Health Service
ONS	Office for National Statistics
OR	Odds Ratios
RH	Relative hazards (estimates resulting from a Cox model)
RR	Relative Risk (resulting from a Poisson model)
UTS	Up-to-standard

APPENDIX II: DATA DEFINITIONS

Age

Since only the year of birth is available in GPRD, age was calculated as the difference between the year of the index date and the birth year. Age was categorised into <40, 40-49, 50-64, 65-74, 75-79, and 80+.

BMI

Body Mass Index was calculated from weight and height information. The closest height, weight and BMI measurements to the index date were used. BMI is calculated using $\text{weight (kg)} / (\text{height (m)} * \text{height (m)})$, for patients aged at least 18 at the date of the height measurement. BMI measurements of <10 or >70 were excluded. BMI was categorised into underweight/normal (<25), overweight (25 - <30), obese (30 - <35), and very obese (≥ 35).

Drinking Status

Alcohol consumption was calculated from records of drinking status, and from searching for alcohol consumption records in the patient's history using a Read code list. Only records from before or on index date were included. The categories were ordered by increasing use of alcohol. For duplicate records on the same day that differed (e.g. Ex-drinker and Teetotaller), the larger value was used (i.e. Ex-drinker). Drinking status was categorised into non-drinker, ex-drinker and drinker.

Index date

For study population 1: the date of the first prescription record of a GnRH agonist in GPRD.

For study population 3: the date of the first medical record of an indication for GnRH agonist treatment in GPRD.

Smoking status

Smoking status was calculated from records of smoking status, and from searching for smoking records in the patient's history using a Read code list. Only records from before or on index date were included. The categories were ordered by increasing use of cigarettes. For duplicate records on the same day that differed (e.g. Ex-smoker and Non-smoker), the larger value was used (i.e. Ex-smoker). Smoking status was categorised into non-smoker, ex-smoker and smoker.

Socioeconomic status (deprivation)

Deprivation was calculated in two ways, using for the postcode of practice and the postcode of the patient. Both of these were mapped at the small area level to the Index of Multiple Deprivation. The Index of Multiple Deprivation combines a number of indicators, chosen to cover a range of economic, social and housing issues, into a single deprivation score for each small area. The indicators are different for England, Scotland, Wales and Northern Ireland, but generally include income, employment, health, and the living environment. The quintiles relate to the country as a whole.

UTS follow up

GPRD practices are identified as up-to-standard once they fulfil certain recording standards. For a patient, UTS follow-up begins from the latest of the patient's registration date and the practice up-to-standard date. UTS follow-up ends at the earliest of the patient's death, transfer out of the practice, or practice last collection date.

APPENDIX III: ICD-10 CODES AND FREE-TEXT

Outcomes

Suicide as cause of death

ICD10 codes from death certificates - ICD10 X60-X84

Admission to hospital due to depression

ICD10 codes identified in HES - F32-F33

Free-text searches

Suicide

The following terms were used to search for records in GPRD free-text for suicide:

- suic
- self
- overdos
- over-dos
- harmful thought

Exposure misclassification

The following terms were used to search for records in GPRD free-text for GnRH prescribing:

- Goserelin
- Zoladex
- Leuprorelin
- Prostag
- Triptorelin
- Decapeptyl
- Buserelin
- Suprefact
- Suprecur
- Nafarelin

- Synarel
- Gonapeptly
- Novgos

APPENDIX IV: TABLES OF RESULTS

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