

Paper

Relationship between age at gonadectomy and health problems in kittens adopted from shelters

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Prepubertal gonadectomy (PPG) is promoted as a way of managing overpopulation in cats, but concerns about PPG and potential health issues still exist. The objective of the present study was to evaluate short-term and long-term health problems in cats subjected to PPG in comparison to gonadectomy at traditional age (TAG). In a prospective clinical trial, 800 shelter kittens aged between approximately 8 weeks and 12 weeks were recruited before adoption and randomly assigned to either the PPG group (gonadectomy performed immediately) or the TAG group (gonadectomy delayed until six months to eight months of age). Short-term health issues included mortality between when kittens arrived at the clinic and up to seven days after they returned to the shelter, as well as the occurrence of various other health issues arising in the first month following adoption. Kittens were followed-up until 24 months of age specifically for feline lower urinary tract disease, urethral obstruction (male cats), lameness, fractures and hypersensitivity disorders with dermatological presentation. In the short term, there were no significant differences between health problems in PPG and TAG kittens. Similarly, no significant differences were observed between treatment groups in terms of the type or number of health issues in the long term. In conclusion, there are no health-related contraindications to advocating PPG strategies in shelter cats. Ideally, PPG should be performed at the shelter facility itself as long as excellent infectious disease control and postoperative clinical observation before adoption are guaranteed.

Introduction

Prepubertal gonadectomy (PPG), defined as gonadectomy between 6 weeks and 16 weeks of age (Root 1999, 2013), is frequently performed in cats in animal shelters in an effort to curtail overpopulation (Looney and others 2008a, Joyce and Yates 2011, Clark 2012, Sparkes and others 2013). Practical and safe anaesthetic and surgical protocols are available for PPG (Aronsohn and Faggella 1993, Faggella and Aronsohn 1993,

Theran 1993, Robertson and others 2003, Joyce and Yates 2011, Bushby 2013, Porters and others 2014a, b); nevertheless, there are still concerns about the effects of PPG on the behaviour and health of domestic cats (Spain and others 2002, Murray and others 2008).

Gonadectomy may lead to an increased risk of feline lower urinary tract disease (FLUTD) (Fennell 1975, Willeberg and Priester 1976, Lekcharoensuk and others 2001, Gunn-Moore 2003). Furthermore, a lack of gonadal hormones negatively affects closure time of selected physes in male (May and others 1991, Houlton and McGlennon 1992, Stubbs and others 1996, Root and others 1997, McNicholas and others 2002, Perry and others 2014) and female cats (Stubbs and others 1996, Root and others 1997). This delay may result in the lengthening of the associated bones (Root and others 1997), thus making growth plates more susceptible to injury (Salmeri and others 1991, Stubbs and others 1996), in particular, to fracture (Root Kustritz 1999). However, the clinical relevance of slower physeal maturation remains unclear (Stubbs and others 1996, Root Kustritz 1999, 2013, Perry and others 2014).

To date, limited research has been performed on the clinical effects following PPG compared with gonadectomy at traditional age (TAG)—only one short-term survey (Howe 1997) and three long-term studies (Stubbs and others 1996, Howe and others 2000, Spain and others 2004). A study by Howe (1997) found that short-term complications (arising within seven days after surgery) were not more frequent following PPG than

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following TAG; however, dogs and cats were evaluated together. Although the risk of developing a medical condition such as FLUTD, urethral obstruction, lameness, fractures or allergic skin diseases was not higher in PPG compared with TAG cats in the published long-term surveys, interpretation of the data is hampered by methodological issues. In two cases, owners were asked to recall the medical history of their cat up to one year previously (Howe and others 2000, Spain and others 2004). In the third study, the sample size was limited (Stubbs and others 1996). Furthermore, in two of the studies PPG was defined as gonadectomy in cats aged less than 24 weeks (Howe and others 2000, Spain and others 2004) rather than less than 16 weeks (Root Kustritz 1999, 2013). Therefore the potential relationship between age at time of gonadectomy and health problems remains to be elucidated, but this is key for PPG to be accepted as a tool to manage the cat population (Stubbs and others 1995, Howe 1997, Joyce and Yates 2011).

This prospective study was part of a large-scale project on early gonadectomy in cats supported by the Belgian government to better familiarise veterinarians and the public with PPG. The aims were to study short-term and long-term health issues following PPG compared with TAG in shelter cats.

Materials and methods

The study protocol was approved by the local Ethical Committee (Faculty of Veterinary Medicine, Ghent University, Belgium) (licence number EC 2010/019 and 2011/077) and the national Deontological Committee (Federal Public Service Health, Food Chain Safety and Environment, Brussels, Belgium), according to the applicable laws and regulations in Belgium and the European Union.

Animals

Between May 2010 and August 2012, 800 healthy kittens were recruited from animal shelters in Flanders, Belgium. Kittens were dewormed and vaccinated at least once against feline parvovirus, feline calicivirus and feline herpesvirus (Aronsohn and Faggella 1993, Looney and others 2008b). Kittens' age was estimated based on their bodyweight and those between 0.7 kg and 1.4 kg, corresponding to an age of 8–12 weeks (Lawler 2008), were enrolled in the study. A thorough physical examination was conducted before the kittens were transported to the clinic of the Faculty of Veterinary Medicine at Ghent University. Littermates were housed together as much as possible to minimise stress and discomfort (Faggella and Aronsohn 1994, Howe 1999).

Kittens were randomly assigned to one of two unequally sized groups. Two-thirds were assigned to PPG and one-third to TAG using a stratified randomisation scheme. A larger group of kittens receiving PPG treatment was established with the goal of obtaining more information about this group. All kittens were microchipped for identification. Kittens belonging to the PPG group were gonadectomised upon assignment to the group. In the TAG group, gonadectomy was postponed until the kittens were six months to eight months of age. The surgical and anaesthetic protocols used are described in detail elsewhere (Porters and others 2014a, b, respectively). After their stay at the clinic, the kittens (PPG and TAG) were returned to the original shelter and offered for adoption. The length of time that the kittens (PPG and TAG) stayed at the clinic was five days from May 2010 to April 2011 (period 1), and was reduced to one day from April 2011 until August 2012 (period 2: April 2011 to April 2012, and period 3: April 2012 until August 2012). The reduction in time spent at the clinic was based on limited surgical and anaesthetic complications being observed. There was no obvious clinical benefit of a prolonged postoperative follow-up period at the clinic. After a stay of one day at the clinic (April until August 2012), the kittens (PPG and TAG) were observed for an additional two days by the shelter staff, before being placed for adoption.

Individuals interested in adopting a kitten included in the project received an information brochure describing the study goals and the effort required from adopters. Adopters were asked

to sign an informed consent form and to provide contact information. The health condition of PPG and TAG cats was evaluated until 24 months of age by means of a web-based survey, a health check-up and regular phone interviews.

Shelter caretakers, shelter veterinarians and adopters were asked to inform the investigator (NP) when a kitten became ill or died shortly after its stay at the clinic for gonadectomy. Owners were also encouraged to immediately report if their cat died or went missing up until 24 months of age.

At the end of the first month after adoption, the owners received an e-mail invitation (and, if necessary, an automatic reminder) to complete a web-based survey created on a dedicated Microsoft Dynamics CRM platform (ESC, De Pinte, Belgium). Paper copies were available to owners without internet access. When the cat reached the age of six–eight months, owners were contacted (via an e-mail invitation or phone) to present their cat to the clinic for a health check-up. During that visit, gonadectomy was performed in the TAG cats.

To reach owners by telephone to acquire information about the health of their cat at 12 months, 18 months and 24 months of age, at least three attempts were made at various times during the day and in the evening, both on weekdays and weekends. If the owner could still not be reached, an e-mail was sent, requesting to contact in due course.

Short-term follow-up

The medical outcomes investigated during short-term follow-up were kitten mortality between when kittens arrived at the clinic and up to seven days after they returned to the shelter, and the occurrence of health issues as reported by the owners in the first month after adoption.

If a kitten died, its cadaver was submitted to the Department of Pathology, Faculty of Veterinary Medicine, Ghent University for full postmortem examination, whenever possible.

Data about the health of the kittens during the first month after adoption were gathered via the web-based survey at the end of the first month following adoption. The inclusion criteria for data analysis were: (1) the kitten was adopted within 30 days after their stay at the clinic (thus limiting the variation in age of kittens to eight weeks), (2) kittens temporarily housed in foster families (rather than traditional shelters) were not adopted by those families, and (3) the survey was completed by the adopter within 14 days of the initial request. Owners were asked whether (1) the cat was still in the household and, if not, what had happened to the cat and (2) whether the cat had been examined by a veterinarian and if so, for which reasons (only health-related problems were included, not preventive medical care such as vaccinations, deworming, etc).

Long-term follow-up

During the health check-up at six–eight months of age and during phone calls at 12 months, 18 months and 24 months of age, cat owners were asked whether the cat was still in the household and whether the cat had been ill during the period of interest (that is, the time interval between two questionnaires). Medical history data of interest were: FLUTD (including signs of haematuria, stranguria and pollakiuria as well as urinary obstruction), lameness (fracture-related or other) and hypersensitivity skin disorders. The consulted veterinarian was contacted for more details regarding FLUTD and for other complex problems that could not be adequately described by the owner. If cats died during the long-term follow-up period, routine postmortem examinations were not requested.

Statistical analysis

For the short-term follow-up, kitten mortality between when kittens arrived at the clinic and up to seven days after they returned to the shelter were analysed using logistic regression with treatment group, sex, period and their interactions as fixed effects. Also, the prevalence of health problems reported in the survey at one month after adoption was analysed using logistic

regression with treatment group, sex, period and their interactions as fixed effects. Non-significant interactions were removed from both analyses. In the case of sparse data, exact inferential techniques were used.

For the long-term follow-up, data about the incidence of FLUTD, urethral obstruction (male cats only), degree of lameness, fractures and hypersensitivity skin disorders were analysed by logistic regression for each medical outcome separately with treatment group, sex, period, and their interactions as fixed effects. Non-significant interactions were removed. In the case of sparse data, exact inferential techniques were used. A response of 1 was noted if at least one episode of a medical outcome was reported for the cat during the follow-up period (minimum 6 months, maximum 24 months). For this analysis, cats not adopted from the shelter, or relinquished or rehomed due to personal reasons before the start of long-term follow-up (six–eight months of age) were excluded.

Statistical analysis was performed with SAS V.9.3 (SAS Institute, USA), using a significance of 5%. Binomial variables were presented as the proportion of kittens (number or percentage) belonging to a specific category.

Results

Eight hundred kittens from 18 animal shelters were recruited between May 2010 and August 2012. Of those, 547 were in the PPG group (female: n=289; male: n=258) and 253 in the TAG group (female: n=125; male: n=128).

Short-term follow-up

Forty-two kittens died between the arrival of the kitten at the Faculty of Veterinary Medicine and the end of the first week after the kitten returned to the shelter (8–13 weeks of age), and there were no significant differences between PPG (31/547; 5.7%) and TAG kittens (11/253; 4.3%) ($P=0.37$). Infectious diseases were deemed to be the cause of most kitten fatalities. Feline panleucopenia virus infection was diagnosed in 11 PPG and two TAG kittens based on histology and immunohistochemistry. Furthermore, this disease was highly suspected in another nine PPG and two TAG kittens, based on clinical signs and the fact that a littermate died of confirmed panleucopenia. In one additional kitten (PPG), postmortem examination and histology indicated enteritis with signs suggestive of panleucopenia, unconfirmed by immunohistochemistry and virus isolation. One female PPG kitten died shortly after surgery because of an intraoperative complication (controlled but excessive blood loss due to inadvertent laceration of the spleen), another kitten (PPG) due to sepsis and two more (PPG) due to interstitial pneumonia based on histological examination, while a viral aetiology was ruled out. Cause of death of the remaining 13 kittens was not investigated, as cadavers were not available for postmortem examination. In six PPG and seven TAG kittens, clinical signs of gastrointestinal pathology or vague clinical signs quickly resulting in death were reported by owners or caretakers, suggesting an underlying viral cause.

Of 539 surveys completed by the adopter at the end of the first month after adoption, only 396 surveys of 275 PPG and 121 TAG kittens between 12 weeks and 20 weeks of age were used for analysis. One hundred and thirty-eight kittens (46.2%) were seen by a veterinarian for one (n=125) or multiple (n=13) medical issues, and there were no significant differences between the PPG (92/275; 33.5%) and TAG (46/121; 38.0%, $P=0.59$) groups. Upper respiratory tract diseases (sneezing, coughing, fever, eye inflammation or infection, tongue ulcers) were the reason given for seeking veterinary assistance in nearly half of the kittens (46 PPG and 23 TAG). In another 46 kittens (28 PPG and 18 TAG), gastrointestinal diseases (vomiting, anorexia, diarrhoea, endoparasitic infestation) were diagnosed. Dermatological conditions (skin infections, fungal diseases, ear mites) were also commonly reported (24 PPG and 6 TAG). Less frequent health problems were: toe fracture (2 PPG), underweight (2 PPG) and stiffness (probably due to viral disease) (1 PPG and 1 TAG).

Long-term follow-up

Long-term follow-up was available for 614 cats (PPG: n=417, TAG: n=197). One hundred and eighty-six cats were lost to follow-up before the beginning of the long-term evaluation due to miscellaneous reasons (Table 1). Information about the medical condition of the cat at 6–8 months, 12 months, 18 months and 24 months of age could be obtained in the majority of cases for each time point (Table 2). The number of cats available per time point decreased towards the end of the study, when 78 more cats (52 PPG, 26 TAG) were lost to follow-up. Death was the reason for dropout in 40 cats (11 cats, 8 cats and 21 cats between 8 months and 12 months, 12 months and 18 months, 18 months and 24 months of age, respectively). The most common cause of death was a road traffic accident (19 PPG, 12 TAG). Rarely, cats died of clinical signs compatible with feline infectious peritonitis (2 PPG, 1 TAG), feline leukaemia virus (1 TAG), liver pathology (1 PPG), unwitnessed trauma (1 PPG) or suspected intoxication (1 PPG, 1 TAG). One kitten (PPG) displayed acute weakness before it died at around 12 months of age. Thirty-eight kittens were lost throughout long-term follow-up (7 cats, 13 cats and 18 cats between 8 months and 12 months, 12 months and 18 months, 18 months and 24 months of age, respectively) because they were missing (17 PPG, 9 TAG) or were rehomed due to owner's allergies or other personal reasons (9 PPG, 2 TAG), or because the cat displayed undesirable behaviour (1 PPG).

The number of cats for which the owner reported health-related issues per time point is depicted in Table 2. The response rate for owners that could be reached was 89.8%, 92.2%, 86.4% and 92.9% at 6–8 months, 12 months, 18 months and 24 months of cat's age, respectively. Throughout long-term follow-up, no significant differences were observed for any medical outcome of interest between treatment groups (Table 3), nor were any significant differences observed for sex and time period (Table 4). The odds ratios provided an indication of the possible impact (<1.0 represents a decrease, >1.0 represents an increase) of each class of the variable compared with a predefined reference value of the same variable on the response under investigation (Table 4). For example, PPG cats were almost twice as likely to develop FLUTD during long-term follow-up compared with TAG cats.

Overall, 10 cats (8 PPG, 2 TAG) were diagnosed with at least one episode of FLUTD, of which five were male cats (4 PPG, 1

TABLE 1: Reasons for dropout of 186 kittens at the beginning of the long-term follow-up at six–eight months of age and the number (%) of cats in the prepubertal gonadectomy group (PPG: n=547) and traditional age gonadectomy group (TAG: n=253)

Reason	PPG n (%)	TAG n (%)
Death	54 (9.9)	23 (9.1)
Within first week upon return to shelter*	31 (5.7)	11 (4.3)
Due to trauma	10 (1.8)	6 (2.4)
Due to infectious diseases†	11‡ (2.0)	5§ (2.0)
Due to other causes	2¶ (0.37)	1** (0.40)
Not returned home	18 (3.3)	6 (2.4)
Returned to shelter or rehomed	6†† (1.1)	0 (0.0)
No participation owner	35 (6.4)	18 (7.7)
Not adopted at six–eight months of age	19 (3.5)	7 (2.8)

*Between the arrival of the kitten at the Faculty of Veterinary Medicine and the end of the first week after the kitten returned to the shelter, main cause of death in postmortem examinations of kittens was infectious diseases

†Suspicion, no postmortem examination performed

‡Clinical signs of feline infectious peritonitis (n=5), upper respiratory diseases (n=2), feline leukaemia virus (n=2), feline panleucopenia virus (n=2)

§Clinical signs of feline infectious peritonitis (n=4) and feline panleucopenia virus (n=1)

¶Unknown (n=1), liver pathology (n=1)

**Intoxication (n=1)

††Reasons: owner's allergy (n=2), movement (n=1), behavioural reasons (n=2), unknown reasons (n=1)

TABLE 2: The number of cats (%) in the prepubertal gonadectomy (PPG) group and traditional age gonadectomy (TAG) group for which data were obtained about their health status at 6 months to 8 months, 12 months, 18 months and 24 months of age and the number of cats with feline lower urinary tract disease (FLUTD), urethral obstruction (tomcats), lameness, fractures and hypersensitivity disorders at each age category

Age (months)	Group	Responders/ population at risk (n cats)	FLUTD	Urethral obstruction*	Lameness	Fractures	Hypersensitivity disorder
6–8	PPG	366/416	0 (0)	0 (0)	5 (1.3)	1 (0.27)	0 (0)
	TAG	185/197	0 (0)	0 (0)	1 (0.54)	0 (0)	0 (0)
12	PPG	382/413	3 (0.79)	1 (0.51)	19 (5.0)	3 (0.79)	5 (1.3)
	TAG	175/191	1 (0.57)	0 (0)	8 (4.6)	4 (2.3)	1 (0.33)
18	PPG	257/291	5 (1.95)	3 (1.6)	11 (4.3)	0 (0)	4 (1.6)
	TAG	85/105	1 (1.18)	1 (1.1)	5 (5.9)	1 (1.2)	1 (1.4)
24	PPG	349/372	4 (1.15)	1 (0.5)	8 (2.3)	0 (0)	4 (1.2)
	TAG	160/176	1 (0.63)	0 (0)	5 (3.1)	0 (0)	3 (0.39)

*Tomcats only.

TAG) that were presented with urethral obstruction. Specifically, two female PPG cats were diagnosed with cystitis before 12 months of age, followed by recurrence of cystitis and surgical removal of bladder stones identified as struvites before 18 months of age. One male TAG cat had an episode of cystitis before 12 months of age and two male PPG cats were diagnosed with one episode of FLUTD before 24 months of age (one with crystalluria, one with cystitis). One male PPG cat had its first episode of FLUTD with obstruction before 12 months and its second episode before 18 months of age. Two other male PPG cats had a urethral obstruction around 18 months of age and one male PPG cat had one at around 24 months of age. Except for the last animal, crystals were evaluated (2 PPG: struvite, 1 PPG: unidentified). One of the male PPG cats with a urethral obstruction before 18 months of age had an episode of FLUTD without obstruction between 18 months and 24 months of age. One male TAG cat had a urethral obstruction at around 18 months of age (plug or crystals not investigated) and an episode of FLUTD (crystalluria without obstruction) at around 24 months of age.

Fifty-eight cats (39 PPG, 19 TAG) had at least one episode of lameness during follow-up. Of these, three PPG and five TAG cats were diagnosed with fractures, all before 18 months of age. One PPG cat experienced two fracture events, one before 6–8 months of age and one before 12 months of age. All fractures were caused by traumatic insults (road traffic accident, heavy object on foot, kick by a horse), which were witnessed in all but one case. Lameness without fractures was reported 56 times in 50 cats (36 PPG, 14 TAG); two probably unrelated episodes of lameness were observed in five of the PPG cats and in one of the TAG cats. Trauma or fighting was reported in 14 PPG and 5 TAG cats. Lameness in one additional PPG cat was likely due to viral polyarthritis. However, in majority of the cases, the cause of lameness was unclear (22 PPG, 8 TAG). Most problems resolved spontaneously or with supportive care (24 PPG, 8 TAG).

In 13 cats (9 PPG, 4 TAG), a hypersensitivity skin disorder was reported. In 8 PPG cats a food hypersensitivity was suspected based on a history of dermatological complaints and/or positive response to a hypoallergenic diet with(out)

immunomodulating therapy (e.g. glucocorticoids). The first signs of food hypersensitivity were encountered before the age of one year in five cases. Around 12 months and 18 months of age, one TAG cat was diagnosed with indolent ulcers and around 24 months of age, one PPG cat and one TAG cat were diagnosed with indolent ulcers. Moreover, around 24 months of age, two TAG cats were also diagnosed with eosinophilic skin diseases.

Discussion

Concerns about effects of PPG on physical development and health in cats are a common reason for veterinarians not to support PPG. The present study was designed to provide short-term and long-term follow-up information on the health consequences in shelter cats following PPG at 8–12 weeks of age compared with TAG at six–eight months of age.

Fatalities between when kittens arrived at the clinic and up to seven days after they returned to the shelter were not significantly higher in neutered kittens (PPG) than in entire kittens (TAG). Causes of death among PPG kittens were not directly related to anaesthesia and/or surgery, and were similar to those among non-operated TAG kittens. Fatalities were mainly caused by infections such as feline panleucopenia virus or by respiratory diseases. Also, in a previously reported study, infectious diseases accounted for the greatest number of fatalities during the seven-day period after PPG (Howe 1997). Similarly, in another report, fatalities observed in kittens in animal care and private homes were mainly due to infectious diseases (Cave and others 2002).

In the present study, to obtain the highest level of standardisation, transport of all kittens (PPG and TAG) was inevitable. Therefore, stress associated with transportation from the shelter to the clinic and the associated change in environment may have facilitated the outbreak of viral diseases in both PPG and TAG kittens enrolled in this study. However, under normal conditions, the higher risk for outbreak of viral diseases would only affect PPG kittens, for they are the only ones undergoing the surgical procedure and early hospitalisation. Such types of stress should obviously be minimised by performing the surgery at a spay/neuter facility in the shelter itself (Howe 1997). Ideally,

TABLE 3: The per cent (%) of cats in the prepubertal gonadectomy (PPG) group and traditional age gonadectomy (TAG) group with feline lower urinary tract disease (FLUTD), urethral obstruction (tomcats), lameness, fractures and/or hypersensitivity disorders during the long-term follow-up (until 24 months of age) without significant differences in type and/or number of health issues between both treatment groups.

	FLUTD	Urethral obstruction*	Lameness	Fractures	Hypersensitivity disorder
PPG (n=417)	8 (1.9)	4 (1.6)	39 (9.4)	3 (0.72)	9 (2.2)
TAG (n=197)	2 (1.0)	1 (0.80)	19 (9.6)	5 (2.5)	4 (2.0)
Overall (n=614)	10 (1.6)	5 (0.81)	58 (9.4)	8 (1.3)	13 (2.1)
P value†	0.44	1.0	0.81	0.11	0.87

*Tomcats only (PPG: n=258, TAG: n=128)

†Logistic regression model (in the case of sparse data, exact inferential techniques were used) with treatment group, sex and period, and interactions among these as fixed effects. Non-significant interactions were removed

TABLE 4: Variables investigated for association with the occurrence of feline lower urinary tract disease (FLUTD), urethral obstruction, lameness, fractures and hypersensitivity disorders in cats gonadectomised prepubertally (PPG) or at traditional age (TAG) during the long-term follow-up (until 24 months of age). The impact of the different variable values compared with the variable reference value (bold) is shown by odds ratios and their respective 95% confidence limits (95% CIs)

Variables	Variable values	FLUTD		Urethral obstruction*		Lameness		Fractures		Hypersensitivity disorder	
		OR (95% CI)	P† value	OR (95% CI)	P† value	OR (95% CI)	P† value	OR (95% CI)	P† value	OR (95% CI)	P† value
Group	TAG	-	0.44	-	1.00	-	0.81	-	0.11	-	0.87
	PPG	1.86 (0.39-8.93)		1.92 (0.21-17.54)		0.93 (0.52-1.67)		0.31 (0.07-1.31)		1.104 (0.333-3.663)	
Sex	Male	-	0.05	-	0.95	-	0.31	-	0.49	-	0.06
	Female	0.21 (0.05-1.02)		<0.01 (<0.01->999.99)		0.75 (0.44-1.30)		0.60 (0.14-2.55)		0.281 (0.076-1.033)	
Period#	Period 3	-	0.34	-	0.60	-	0.19	-	0.64	-	0.96
	Period 1	5.26 (0.58-47.62)		>999.99 (<0.01->999.99)		1.92 (0.93-3.97)		0.36 (0.039-0.36)		0.979 (0.214-4.484)	
	Period 2	3.86 (0.44-33.33)		>999.99 (<0.01->999.99)		1.30 (2.60-0.65)		0.65 (0.14-3.00)		1.160 (0.320-4.219)	

*Male cats only (PPG: n=258, TAG: n=128)

†Logistic regression model (in the case of sparse data, exact inferential techniques were used) with treatment group, sex and period, and interactions among these as fixed effects. Non-significant interactions were removed

#The length of time that the kittens (PPG and TAG) stayed at the Faculty was five days from May 2010 to April 2011 (period 1), and one day from April 2011 until August 2012 (period 2: April 2011 to April 2012, and period 3: April 2012 until August 2012)

sterilised kittens should be observed in their familiar shelter environment for 48 hours postoperatively to detect and control pain or discomfort, and to treat any diseases before the kittens are adopted. Observations such as anorexia, vomiting, diarrhoea and upper respiratory tract diseases in these first days were recorded at the clinic and/or shelter as being present or absent. Due to the lack of detailed information about these miscellaneous diseases acquired from some shelters and the self-limiting nature of most of them, it was decided not to report those data in the current study.

Throughout the first month after adoption, nearly one-third of each group experienced at least one health problem, although it was often mild and temporary. These findings are in accordance with previous studies about health problems in cats and dogs during the first month after adoption from a shelter (Neidhart and Boyd 2002, Lord and others 2008). Not unexpectedly, upper respiratory tract diseases were the most commonly reported reasons for seeking veterinary care. The reported prevalence of upper respiratory tract diseases in a study involving eight shelters in California (USA) varied from 8% to 38% and kittens below three months of age were at higher risk of developing upper respiratory tract diseases (Bannasch and Foley 2005). Moreover, cats can be carriers of one or more infectious agents related to upper respiratory tract diseases and latent infections can be reactivated in response to stress, resulting in clinical disease (Gourkow and others 2013). Stress induces immunodeficiency and results in vulnerability to various infectious diseases, as suggested by Pesavento and Murphy (2014). In addition, kittens are more vulnerable to infectious diseases than immunised adult animals for several reasons. Due to maternal antibodies, their response to vaccination will be incomplete (Day and others 2010). Infectious disease control (such as implementing vaccination protocols, cleaning/disinfecting protocols and hand hygiene) is therefore essential in shelters (Hurley 2005, Newbury and others 2010) and in neutering facilities (Howe 1997, Looney and others 2008a). Also, adopters should be notified about the susceptibility of kittens to illness, the high risk of contagious disease exposure in shelters, and the stress associated with novel (non-)social environments after adoption. Veterinarians have an important role in reassuring and educating the adopters about the health of their shelter kitten by explaining the nature of mostly mild and/or self-limiting infections and by treating those infections (Scarlett and others 2002). Therefore, adopters should be encouraged or required via contract to present their cat to a veterinarian shortly after the adoption, in particular since it is established that disease in the immediate postadoption period is correlated with animal relinquishment (Wells and Hepper 1999).

Notwithstanding the methodological improvements to obtain accurate information such as prospective design and data collection at several time points, the current findings did not differ from those of previous long-term studies (Stubbs and others 1996, Howe and others 2000, Spain and others 2004). In the current long-term follow-up (6-24 months of age), no association could be identified between age at the time of gonadectomy and the incidence of FLUTD, urethral obstruction, fractures, lameness and hypersensitivity skin disorders.

The finding that PPG was not associated with higher risk of urethral obstruction in entire male cats is in accordance with the observation that the urethral diameter at 22 months of age was not significantly different among male cats left entire, and those neutered at seven weeks or at seven months (Root and others 1996a). Also, at 10 months of age, male cats left entire or neutered at five months of age had a similar urethral diameter, irrespective of testosterone supplementation in neutered cats (Herron 1972). In one epidemiological survey, it was shown that neutered cats were at higher risk for FLUTD, but the age at time of gonadectomy (i.e. <6 months or late i.e. >11 months) had no effect on the development of FLUTD (Walker and others 1977).

The incidence of lameness or fractures did not differ significantly between PPG compared with TAG cats in the current study. It is well documented that time of closure of specific

growth plates differs significantly between neutered and entire cats (May and others 1991, Perry and others 2014). However, times of closure of growth plates were found not to differ significantly in cats neutered at seven weeks or seven months in two previous studies (Stubbs and others 1996, Root and others 1997). In the present study, the reported episodes of lameness in PPG and TAG cats were generally self-limiting and had a traumatic or unknown cause. These findings suggest that, even if physal closure time would be delayed in PPG compared with TAG cats, it seems unlikely to be clinically relevant. In only one report on 26 cats, early age neutering before six months was reported as a risk factor for spontaneous femoral capital physal fractures in adult cats (McNicholas and others 2002); however, these cats were also overweight. Overweight in cats is a known risk factor for lameness (Scarlett and Donoghue 1998) as well as for traumatic fractures at the capital femoral epiphysis (Craig 2001). Unlike the plethora of studies comparing obesity in gonadectomised versus entire animals regardless of time of gonadectomy (Fettman and others 1997, Robertson 1999, Allan and others 2000, Martin and others 2001, Lund and others 2005, Colliard and others 2009, Courcier and others 2010), few studies have specifically addressed the relationship between age at time of gonadectomy and the development of overweight in cats (Stubbs and others 1996, Root and others 1996b, Alexander and others 2011). It is well established that gonadectomy is one of the important predisposing factors for the development of overweight and obesity in cats (Robertson 1999, Lund and others 2005, Colliard and others 2009, Courcier and others 2010, Joyce and Yates 2011). Yet studying overweight in cats is hampered by its multifactorial nature, to which numerous uncontrolled variables such as diet, exercise and genetics contribute (Joyce and Yates 2011). In a subset of kittens enrolled in the present study, plasma leptin concentrations were studied in addition to recording bodyweight and body condition score. It was observed that plasma leptin concentrations in cats at six–eight months of age were higher in neutered PPG cats compared with sexually entire TAG cats (manuscript submitted). No significant differences in hypersensitivity skin disorders between PPG and TAG cats were observed. It should be noted that, although the incidence in the present study was low, it might still be overestimated since diagnoses were mostly suspected rather than based on exclusion of other pruritic viral, fungal, bacterial or parasitic diseases (Hobi and others 2011, Favrot and others 2012). Based on the current findings, it seems unlikely that age of gonadectomy is associated with feline hypersensitivity skin disorders. Yet Spain and others (2004) suggested an association existed between allergic skin diseases, and Howe and others (2000) between problems of the integumentary system (including minor skin allergies), and early gonadectomy.

Finally, some additional comments should be made. A follow-up period of 24 months certainly does not reflect the life span of cats. Nevertheless, it does permit evaluation of the health of kittens and junior cats into adulthood (Hoyumpa Vogt and others 2010). Especially for conditions such as FLUTD, with an increased risk between two years and seven years of age (Willeberg and Priester 1976, Lekcharoensuk and others 2001), a much longer follow-up period would be ideal. It should also be noted that in the present study the occurrence of any investigated disease in the long-term follow-up was relatively rare ($\leq 13/614$ cats ($\leq 2.1\%$) for each condition), therefore the statistical power for finding significant differences between PPG and TAG cats was rather low. Around 1,605 PPG and 827 TAG male cats should be studied to be able to document a significant difference of 2% between both treatment groups when comparing urethral obstruction with a power of 80%.

Conclusion

The results of the present study do not indicate that PPG in cats increases risk of health issues until 24 months of age compared with TAG. Ideally, gonadectomy should be performed at the shelter facility to avoid stress associated with transport to

another facility and environmental changes. Successful PPG strategies require optimal infectious disease control at the shelter and spay/neuter facility and postoperative clinical observation of the kittens in their familiar shelter environment before adoption.

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