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SPONTANEOUSLY ARISING DISEASE: REVIEW ARTICLE

Obesity and Associated Comorbidities in People and Companion Animals: A One Health Perspective

**M. Chandler^{*}, S. Cunningham[†], E. M. Lund[‡], C. Khanna[§],
R. Naramore[¶], A. Patel^{||} and M. J. Day[#]**

** Vets Now Referrals, Glasgow, Scotland, UK, † Hubert Department of Global Health, Emory University, Atlanta, Georgia, ‡ Banfield Pet Hospital, 18101 Southeast 6th Way, Vancouver, Washington, § Ethos Veterinary Health, Woburn, Massachusetts, ¶ The Oncology Service, Springfield, Virginia, || American Cancer Society, Atlanta, Georgia, USA and # School of Veterinary Sciences, University of Bristol, Langford, North Somerset, UK*

Summary

This article reviews the biology, prevalence and risks for obesity in people and companion dogs and cats, and explores the links between obesity and diabetes mellitus and cancer across these species. Obesity is a major healthcare problem in both human and veterinary medicine and there is an increasing prevalence of obesity in people and pets. In people and animals, obesity is a complex disorder involving diet, level of physical activity, behavioural factors, socioeconomic factors, environment exposures, genetics, metabolism and the microbiome. Pets and people share a number of obesity-related comorbidities. Obesity is a major risk factor for type 2 diabetes mellitus in people and in cats, but this association is not recognized in dogs. Obesity is a recognized risk factor for a number of human cancers, but there are fewer data available describing this association with canine neoplastic disease. One approach to addressing the problem of obesity is by taking a ‘One Health’ perspective. Comparative clinical research examining shared lifestyle and environmental risk factors and the reasons underlying species differences should provide new perspectives on the fundamental biology of obesity. One Health programmes involving human healthcare professionals and veterinarians could help address obesity with simple interventions at the community level.

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Keywords: cat; dog; human; obesity; One Health

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Correspondence to: M. J. Day (e-mail: m.j.day@bristol.ac.uk).

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Introduction

In developed nations, people and small companion animals share, to varying degrees, their lifestyle and environment. This partnership comes with myriad implications for health and well-being, including high rates of type 2 diabetes mellitus, cardiovascular disease and certain cancers. What opportunities exist to leverage this intimate relationship, to mitigate shared risk and to improve the health status of people and companion animals? ‘One Health’ provides a compelling framework to create understanding and to formulate solutions (Day, 2010; Sandoe *et al.*, 2014). The One Health perspective encourages coordinated and collaborative action by human and veterinary healthcare professionals to address health problems common to man and animals. An excellent candidate problem for a One Health approach is that of obesity, which has become a major health issue in people and small companion animals. In this review, we present what is currently known about the prevalence and risks for obesity in pets and people, discuss comparative aspects of selected obesity-associated comorbidities and put forward ideas to aid future research and interventions to encourage healthy behaviours.

Obesity is defined as the accumulation of excess body fat. In small companion animals, due to species, breed and age variation, measurement and subsequent diagnosis of an overweight state and obesity is complex. The most widely adopted procedures are various forms of morphometry, such as dimensional evaluation and body condition scoring, where measured parameters are used to estimate body composition. Dimensional evaluation involves the correlation of a measurement of length (e.g. the head, thorax or limb) or girth (i.e. around the ribcage) with lean body mass or fat mass (Stanton *et al.*, 1992; Hawthorne and Butterwick, 2000). These techniques have led to the development of a feline body mass index (BMI) (Hawthorne and

Butterwick, 2000); however, variation between canine breeds has made the development of a similar system for dogs problematic (Burkholder, 1994). A number of body condition score (BCS) schemes have been devised (Laflamme, 1997a,b; German *et al.*, 2006), all of which are subjective and semiquantitative and involve visual and tactile assessment of characteristics that correlate with abdominal and subcutaneous fat (e.g. the rib cage, dorsal spinous processes and waist). Definition of overweight and obesity used across research studies is, to some degree, non-standardized as a result.

Categories of weight status in people are most often assessed by BMI. BMI is an easy-to-obtain measure of weight accounting for height and is estimated as weight (kg)/height (m)². BMI correlates equitably with direct measures of body fat (<http://www.cdc.gov/obesity/adult/defining.html>). For adults, a BMI ≥ 25 but < 30 , is used in most populations to define overweight and a BMI of ≥ 30 is used to define obesity. For children, to account for growth, weight status is relative to age and sex. In the USA, BMI at ages 2–19 years is compared with age- and sex-specific percentiles on the Centers for Disease Control and Prevention (CDC) growth charts and obesity is defined as a BMI \geq the 95th percentile for age and sex (<http://www.cdc.gov/obesity/childhood/defining.html>).

Prevalence and Trends for Obesity

For dogs, the population prevalence of overweight and obesity has been estimated at 19.7–59.3% (McGreevy *et al.*, 2005; Lund *et al.*, 2006; Hill, 2009; Courcier *et al.*, 2010a; Corbee, 2013; Mao *et al.*, 2013) and for cats at 11.5–52% (Burkholder and Toll, 2000; Lund *et al.*, 2005; German, 2006; Hill, 2009; Courcier *et al.*, 2010b, 2012; Cave *et al.*, 2012; Corbee, 2014). In a general veterinary practice population in the USA, followed over a 5-year period from 2007 to 2011, overweight and obesity increased by 37% in dogs and 90% in cats (Banfield, 2012)

reflecting the increasing trend in prevalence for human obesity.

Surveys in the USA have reported that in 2011–2014, more than a third of adults (36.5%) had obesity (Ogden *et al.*, 2015). Obesity is higher among American adults aged 40–59 years (40.2%) and adults aged ≥ 60 (37.0%) than among adults aged 20–39 years (32.3%) (Ogden *et al.*, 2015). In 2011–2014, one-sixth of American children and adolescents aged 2–19 years (17.0%) had obesity.

Risk Factors for Obesity

Risk Factors in Small Companion Animals

Dogs and cats share some but not all risk factors for overweight and obesity. Genetic risk for the disease manifests in higher risk for particular canine (e.g. Labradors and golden retrievers) and feline breeds (e.g. Manx and domestic shorthair) (Edney and Smith, 1986; Lund *et al.*, 2005, 2006; German, 2006; Corbee, 2013, 2014). Other risk factors include gender, neutering status and middle age. Middle-aged neutered female dogs are most likely to be overweight or obese (Kronfeld *et al.*, 1991; McGreevy *et al.*, 2005; German, 2006; Laflamme, 2006; Lund *et al.*, 2006), while middle-aged neutered male cats are most likely to be overweight or obese (Kronfeld *et al.*, 1991; Scarlett *et al.*, 1994; Lund *et al.*, 2005; German, 2006; Laflamme, 2006; Courcier *et al.*, 2010b, 2012; Cave *et al.*, 2012; Serisier *et al.*, 2013; Corbee, 2014). Obesity risk associated with neutering is due to a combination of decreased energy requirements after neutering and an increase in food consumption (Fettman *et al.*, 1997; Kanchuk *et al.*, 2003). Less is understood about how the level of exercise and activity in dogs and cats relates to obesity. For dogs, reduced daily exercise has been associated with obesity (Bland *et al.*, 2009; Courcier *et al.*, 2010a), as has limited or no outdoor activity for cats (Rowe *et al.*, 2015).

Population-level associations have also been shown between obesity and comorbid conditions. Diseases found concurrently with overweight or obesity include arthritis, endocrine dysfunction (e.g. hypothyroidism, hyperadrenocorticism), cruciate ligament rupture, lower urinary tract disease, oral disease, diabetes mellitus, pancreatitis and neoplasia (Hess *et al.*, 1999; Lund *et al.*, 2005; Lund *et al.*, 2006; Laflamme, 2006; Marshall *et al.*, 2009). Anaesthetic risk has also been reported to be increased in overweight or obese dogs (German, 2006). Some of these associations are likely to be causal (e.g. canine hypothyroidism) and some are the result of excess body condition (e.g. canine

pancreatitis, feline diabetes mellitus). Longevity for people at a healthy body weight is greater than for those who have obesity (Kolonin *et al.*, 2004; Houston *et al.*, 2009). Evidence suggests that this may also be true for dogs (Kealy *et al.*, 2000).

Diet and nutrition play a role in overweight and obesity in people and pets. High-fat diets are associated with overweight or obesity in dogs (Laflamme, 2006). The source of food (commercially prepared versus home-made) was not a significant factor for canine obesity in one study (Kienzle *et al.*, 1998), but a non-commercial source of diet was a risk factor in another study (Mao *et al.*, 2013). The price of pet food has been found to be associated with obesity; owners of obese dogs are more likely to indicate the importance of inexpensive foods (Kienzle *et al.*, 1998). Obesity has also been associated with the number of meals and snacks fed and feeding of kitchen/table scraps, fresh meat and commercial treats for dogs (Kienzle *et al.*, 1998; Bland *et al.*, 2009; Sallander *et al.*, 2010) as well as feeding *ad libitum* in cats (Courcier *et al.*, 2010b).

Human-related (i.e. pet owner) risk factors for canine and feline obesity include owner household income and exercise habits (Kienzle *et al.*, 1998; Courcier *et al.*, 2010a). Owners of overweight or obese dogs have a lower net income than owners of normal weight dogs and are less likely to participate in regular exercise (Kienzle *et al.*, 1998; Courcier *et al.*, 2010a).

Owner's age was associated positively with increased risk for pet overweight and obesity (Courcier *et al.*, 2010a). Some of the factors known to protect cats and dogs from overweight and obesity relate to positive aspects of the human–animal bond. While overweight and obesity in cats is associated with a close bond between the owner and their pet (Kienzle *et al.*, 2001; Kienzle and Bergler, 2006); this result is not the same for dogs (Kienzle *et al.*, 1998), suggesting that the character of the relationship is key. Owners of cats of normal weight played with their cat more often than owners of overweight or obese cats and felt that the cat invited play more often and played with a wider variety of objects (Kienzle and Bergler, 2006). Access to parks and nature reserves was rated as more important for dog owners as compared with non-dog owners. In addition, dog-owners felt they had more social support from family to walk and do other forms of physical activity (Cutt *et al.*, 2008).

Risk Factors in People

Excessive accumulation of adipose tissue in people is generally caused by an imbalance between energy

expenditure and energy intake. However, multiple individual characteristics (e.g. genetics, health status including sleep and stress, medication use, microbiome and knowledge) and factors relating to the family and social environments (e.g. peer pressure and norms), institutions (e.g. work sites, parks and community retail) and macropolicies (e.g. federal, state and local policies that alter access, availability and affordability) can affect behaviours, energy intake, metabolism and expenditure. Other reviews have discussed how factors intersect at various levels (Institute of Medicine, 2005, 2012).

Diet, as it relates to excess calories, is a modifiable factor in weight gain. An approach for healthy weight maintenance is to replace lower-calorie nutrient-dense foods with intake of high-calorie low-nutrient foods. The latter are often those higher in water and fibre, which can aid satiety. The evidence review conducted for the latest US 2015–2020 Dietary Guidelines found that there was moderate evidence that diet patterns that are ‘higher in vegetables, fruits and whole grains; include seafood and legumes; are moderate in dairy products (particularly low and non-fat dairy) and alcohol; lower in meats (including red and processed meats) and low in sugar-sweetened foods and beverages and refined grains are associated with favourable outcomes related to healthy body weight or risk of obesity’ (Dietary Guidelines Advisory Committee, 2015).

Another modifiable risk factor for weight gain is insufficient energy expenditure due to physical inactivity (Strong *et al.*, 2005; Physical Activity Guidelines Advisory Committee, 2008). Sedentary behaviours may be an additional risk factor for weight gain independent of physical activity. These behaviours include sitting and immobile behaviours, with the one most studied being television (TV) watching, but with new research emerging on other screen-time behaviours. Possible mechanisms for the influence of TV on weight gain in people include poor dietary behaviours while watching TV, the replacement of physical activity and unhealthy food purchases and intake due to marketing exposure during commercials (Woodward-Lopez *et al.*, 2006).

An additional factor that may be related to obesity risk is the role of the microbiome. The quality and composition of diet and an individual’s genetic endowments may impact on the types of microbes that exist in the gastrointestinal tract, which in turn can alter energy utilization (Patterson *et al.*, 2016). Another area of research is the role of environmental chemicals in weight gain. Chemicals can be passed on from mother to child during pregnancy and breastfeeding, ingested in foodstuffs or taken up through inhalation or dermal exposure. Research is emerging

which reports that some chemicals may disturb the endocrine system and potentially change metabolic feedback and metabolism impacting on energy balance (Heindel *et al.*, 2015).

Obesity-associated Comorbidities: Diabetes Mellitus

Diabetes mellitus is a serious health condition across species. Diabetes may be classified based on pathophysiological mechanisms as type 1, which is characterized by loss or destruction of pancreatic insulin-producing β cells, and type 2, which is characterized by insulin resistance and dysfunctional β cells. Numerous human studies have linked type 2 diabetes with obesity (Dietz, 1998; Luder *et al.*, 1998; Must and Strauss, 1999; Fagot-Campagna *et al.*, 2000, 2001; Ge *et al.*, 2001; Wang and Dietz, 2002; Friedlander *et al.*, 2003; Must and Anderson, 2003; Haines and Neumark-Sztainer, 2006).

Diabetes Mellitus in Dogs

Nearly all diabetic dogs have type 1 diabetes and are insulin dependent at the time of diagnosis (Panciera *et al.*, 1990). The rate of diagnosis of diabetes mellitus in dogs is approximately 0.6% (Guptill *et al.*, 2003). Several breeds (e.g. Australian terriers, Samoyeds, miniature Schnauzers, miniature and toy poodles) are at higher risk (Chastain *et al.*, 2001; Guptill *et al.*, 2003), indicating a likely genetic basis. Secondary diabetes, which is carbohydrate intolerance secondary to concurrent insulin antagonistic disease or medications, is recognized in the dog; this includes dioestrus or pregnant bitches with diabetes due to progesterone-related insulin resistance.

As diabetes in dogs is generally due to a lack of insulin-producing pancreatic β cells, obesity does not cause diabetes mellitus; however, obesity does decrease insulin sensitivity in dogs and can therefore affect diabetic control (Panciera *et al.*, 1990).

Diabetes Mellitus in Cats

Type 2 diabetes is estimated to be present in >80% of cats with diabetes. Feline type 2 diabetes is characterized by insulin resistance, variable loss of insulin secretion and amyloid deposition in the pancreatic islets. The prevalence of diabetes in cats is thought to be increasing. In the USA, one study reports that feline diabetes has increased from 0.08% to 1.2% in 30 years (Prah *et al.*, 2007) and a prevalence of 0.4% has been recorded in the UK (McCann *et al.*, 2007). Risk factors for type 2 diabetes include obesity and increasing age (Rand, 1997; Baral *et al.*, 2003; McCann *et al.*, 2007). Most affected cats are >8

years of age, and most commonly between 10 and 12 years old, when they get diabetes (Rand, 1997; McCann *et al.*, 2007; Lederer *et al.*, 2007). This is also the peak age for obesity. Other risk factors in cats include prior administration of corticosteroids, male gender, being neutered and, in Australia and the UK, being of the Burmese breed (Lederer *et al.*, 2007; McCann *et al.*, 2007).

In domestic shorthair cats, a polymorphism of the melanocortin 4 receptor (*MCR*) gene is associated with the development of diabetes mellitus in overweight cats, similar to what is found in people. This gene is associated with energy balance and appetite regulation (Focada *et al.*, 2014). The increased prevalence of diabetes mellitus in Burmese cats also indicates a likely genetic basis (O'Leary *et al.*, 2013).

Obesity or overweight body condition is the most recognized risk factor for type 2 diabetes mellitus (Baral *et al.*, 2003; McCann *et al.*, 2007), although some cats with diabetes present with a history of weight loss. Obese cats are several times more likely to become diabetic than cats of normal weight because obesity causes insulin resistance (i.e. decreased sensitivity to insulin) (Rand *et al.*, 2004). Insulin sensitivity decreases by >50% in obese cats compared with lean cats (Chastain and Panciera, 2002). An increase in BCS from 5/9 to 6/9 in growing kittens decreased insulin sensitivity (Haring *et al.*, 2013) and the gain of even 1 kg in an average-sized cat may decrease insulin sensitivity by 30% (Hoenig *et al.*, 2007). Cats initially compensate well for insulin resistance and do not show elevated serum glucose concentrations. Eventually, in some cats, the function of the pancreatic β cells decreases and they do become overtly diabetic.

Several aspects of obesity likely contribute to decreased insulin sensitivity. Adipokines are metabolically active substances secreted from the fat mass, which act systemically or locally to influence metabolic reactions. Increased fat mass is thought to contribute to dysregulation of adipokine production (Kil and Swanson, 2010). Adiponectin is an adipokine that decreases in most species, including cats, with an increase in fat mass (Ishioka *et al.*, 2009). Adiponectin affects the regulation of carbohydrates and lipid metabolism. Adiponectin secretion is stimulated by insulin and enhances insulin sensitivity and increases glucose uptake via glucose transporter type 4 (GLUT4) molecules. GLUT4 expression is decreased during the development of obesity in cats (Brennan *et al.*, 2004) and it also increases fat and carbohydrate oxidation in peripheral tissues, suppresses hepatic gluconeogenesis and inhibits the inflammatory response (Ishioka *et al.*, 2009). Similarly, low adiponectin is associated with progression to type 2 diabetes in obese people.

In contrast, in a study of dogs, serum adiponectin concentrations were not found to be associated with insulin sensitivity, and adiponectin levels are not always associated as directly with body fat in dogs as in people and cats (Verkest *et al.*, 2011). It may be that the differences in adiponectin in dogs compared with people and cats contribute to type 2 diabetes mellitus being less common in dogs.

Many studies of insulin sensitivity in obese dogs have used the 'obese dog model', in which research dogs gain weight due to a high fat diet, often including saturated fats such as lard (Kley *et al.*, 2009). A study examining the effect of types of fat compared inclusion of a saturated fat (lard) to polyunsaturated fat (corn oil) and showed that the lard diet increased circulating insulin and decreased insulin sensitivity, while corn oil did not have an effect on either parameter (Truett *et al.*, 1998). A study in cats fed a diet supplemented with omega-3 fatty acids showed that increased serum concentrations of the omega-3 fatty acid docosahexaenoic acid were associated directly with increased concentrations of adiponectin in obese cats (Mazaki-Tovi *et al.*, 2011).

Concerns have been raised that the feeding of dry diets, which are often higher in carbohydrates than are canned diets, may contribute in the risk of type 2 diabetes mellitus in cats. While the data from various studies are conflicting, it appears that the feeding of dry diets and carbohydrates *per se* are not significant risk factors for diabetes for cats of normal weight (Backus *et al.*, 2007; Slingerland *et al.*, 2009), with the possible exception of Burmese cats in the UK and Australia. Body weight gain due to excess calorie intake is more likely than the type of diet to induce a pre-diabetic condition of insulin resistance and secretion dysfunction.

Diabetes in People

Human diabetes is generally the result of functional or physical loss of β cells. Through the reduced number or capacity of its β cells, the pancreas either does not produce sufficient insulin or is not able to effectively use the insulin that is produced. This can result from an autoimmune process, which generally underlies type 1 diabetes, and insulin resistance, which generally underlies type 2 diabetes (Alberti and Zimmet, 1998; Tuomi, 2005). Type 1 and type 2 diabetes often occur in the same families, suggesting an underlying shared genetic susceptibility (Tuomi, 2005).

Type 1 diabetes is characterized by deficient insulin production and patients must administer insulin daily. Type 2 diabetes results from the body's ineffective use of insulin or need for insulin above the capacity produced by the body, due to obesity and physical

inactivity. Type 1 diabetes has generally been diagnosed in children and type 2 in adults, although type 2 is now also being observed in children. Both result in hyperglycaemia, which damages the body, especially the nerves and blood vessels (World Health Organization, 1999). Therefore, diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.

A third type of diabetes, gestational diabetes, is hyperglycaemia during pregnancy at levels above normal, but below those of diabetes. Gestational diabetes is usually at least temporarily resolved after delivery, although it is associated with complications during pregnancy and delivery and higher risk of type 2 diabetes in the mother and child (World Health Organization, 2013).

In 2014, worldwide 422 million people were estimated to have diabetes, up from 108 million in 1980 (World Health Organization, 2016). In the USA, the number of people with diabetes more than tripled from 8.5 million in 1990 to 29 million in 2014 (Ali *et al.*, 2014; Centers for Disease Control and Prevention, 2015). Levels are highest in the USA and other Western countries, but the prevalence is rising fastest in middle- and low-income countries. Diabetes leads to considerable morbidity, mortality and cost; it is the leading cause of adult-onset blindness, kidney failure and non-traumatic limb amputations. In the USA, it is the seventh leading cause of death (Centers for Disease Control and Prevention, 2014) and globally 1.5 million deaths were attributed to diabetes in 2012 (World Health Organization, 2016). Diabetes is also a leading driver of medical expenditures (Thorpe *et al.*, 2010); in the USA in 2012, diabetes was associated with \$245 billion in health-care expenditure and productivity losses (American Diabetes Association, 2013).

The majority of people with diabetes have type 2 diabetes. While the prevalence of type 1 versus type 2 diabetes is difficult to calculate, type 1 has been estimated to make up about 5% of diabetes cases in the USA (Menke *et al.*, 2013). The prevalence of type 1 diabetes varies across populations (Tuomi, 2005).

Links Between Obesity and Diabetes in People. Overweight and obesity are prevalent in people with both type 1 and type 2 diabetes. Obesity is the leading risk factor for type 2 diabetes, but also increases the risk for developing type 1 diabetes and gestational diabetes (Dietz, 1998; Luder *et al.*, 1998; Must and Strauss, 1999; Fagot-Campagna *et al.*, 2000, 2001; Ge *et al.*, 2001; Wang and Dietz, 2002; Friedlander *et al.*, 2003; Must and Anderson, 2003; Haines and Neumark-Sztainer, 2006; Chu *et al.*, 2007; Polsky and Ellis, 2015).

Obesity also increases morbidities associated with both types of diabetes.

The strong links between obesity and diabetes begin during the early stages of human development. A woman's pre-pregnancy obesity is a risk factor for her child developing obesity and diabetes (Christoffel *et al.*, 2012) as a mother's pre-pregnancy weight is associated with fetal insulin resistance, which in turn is associated with fetal adiposity. Newborns of obese mothers have greater percent body fat and insulin resistance (Reece, 2008; Catalano *et al.*, 2009). At the same time, mothers with diabetes are more likely to have children with obesity (Metzger, 2007; Metzger *et al.*, 2009). Children exposed to maternal diabetes *in utero* are at greater risk of developing obesity and abnormal glucose metabolism during childhood, adolescence and adulthood (Metzger, 2007). Maternal glucose is associated with neonatal adiposity, likely through fetal insulin production (Metzger *et al.*, 2009). Fetal hyperinsulinaemia, which is related to maternal glycaemia, is associated linearly with birthweight (Kohl and Hobbs, 1998; Dabelea *et al.*, 2008; Christoffel *et al.*, 2012). By the time they are 14–17 years old, children of mothers with gestational diabetes have BMIs on average 3.7 points higher than children whose mothers did not have gestational diabetes (Silverman *et al.*, 1998).

Even beyond the early developmental periods, obesity in childhood and adulthood continue to be risk factors for type 2 diabetes. Young onset of type 2 diabetes is a well documented consequence of obesity (Dietz, 1998; Luder *et al.*, 1998; Must and Strauss, 1999; Fagot-Campagna *et al.*, 2000, 2001; Ge *et al.*, 2001; Wang and Dietz, 2002; Friedlander *et al.*, 2003; Must and Anderson, 2003; Haines and Neumark-Sztainer, 2006). Obese children have about a five times higher risk of developing diabetes in childhood (Must and Strauss, 1999; Fagot-Campagna *et al.*, 2000). Hospital discharges of youths with obesity-related diseases are rising, with the most frequent comorbidities being asthma and diabetes (Wang and Dietz, 2002).

A nationally representative study from the USA showed that obese 18-year-old boys and girls could expect to live 14 and 19 fewer years, respectively, without developing diabetes compared with their normal weight classmates (Cunningham *et al.*, 2011). While life expectancy at age 18 years in the USA increased considerably between the 1980s and the 2000s, diabetes-free life expectancy decreased by 1.7 years for men and 1.5 years for women. The increasing share of life spent with diabetes was due to the fact that the proportion of 18-year-olds who would develop diabetes in their lifetime increased by

almost 50% among women and almost doubled among men. Notably, it was only individuals with obesity who experienced losses in diabetes-free life expectancy during this period, estimated at -5.6 years for men and -2.5 years for women, highlighting the relevance of obesity as a risk factor with clear and serious health consequences at the population level (Cunningham *et al.*, 2011).

Obesity-associated Comorbidities: Cancer

Numerous biological mechanisms have been proposed that may link obesity with a higher risk of various types of cancer. A new review finds that at least 13 cancers have sufficient evidence for a cancer-preventive effect of avoidance of weight gain (Lauby-Secretan *et al.*, 2016). Systemic mechanisms that may explain associations across types of cancer involve excess adiposity and increases in sex steroid hormones, growth factor production and chronic insulinaemia (Calle and Kaaks, 2004). Furthermore, adipose tissue acts as an active endocrine organ that releases various hormones (e.g. adipokines) involved in energy balance, lipid metabolism and insulin regulation including leptin, adiponectin, tumour necrosis factor- α and resistin (Rajala and Scherer, 2003). In an obese state, these adipokines are dysregulated, leading to imbalances in metabolic response and development of conditions such as hyperinsulinaemia.

Excess body weight has also been associated with increased insulin levels, which is associated with risk of cancers including those of the endometrium, colon and pancreas (World Cancer Research Fund, 2007). Insulin itself may promote neoplastic growth, but insulin also promotes the production of insulin-like growth factor (IGF)-1, which is involved in cell proliferation. Both insulin and IGF-1 have been shown *in vitro* to promote cell proliferation and inhibit apoptosis and enhance metastasis (Ish-Shalom *et al.*, 1997; Khandwala *et al.*, 2000).

Insulin also has effects on the production and availability of sex steroid hormones such as androgens, progesterone and oestrogens in men, women and dogs. Excess body weight, through the effects of insulin and directly, is associated with the synthesis and bioavailability of sex steroid hormones. In both men and women, excess body weight is associated with a decrease in sex hormone-binding globulin (SHBG), a binding protein with a high specific affinity for oestradiol and testosterone (Calle and Kaaks, 2004). Lower SHBG levels result in increased levels of unbound, bioavailable sex hormones. Higher levels of sex hormones, primarily oestradiol and progesterone, have been shown to be associated with higher levels of

postmenopausal breast and endometrial cancer; furthermore, clinical studies have shown that these hormones play a central role in cell proliferation in these tissue types (Calle and Kaaks, 2004).

An obese state is also associated with chronic inflammation that can lead to increased cell proliferation, inhibit apoptosis and induce angiogenesis (World Cancer Research Fund, 2007). Chronic inflammatory conditions such as Barrett's oesophagus or non-alcoholic fatty liver disease have been locally associated with risk of oesophageal cancer and liver cancer, respectively (World Cancer Research Fund, 2007). Thus, numerous mechanisms, both systemic and local, may explain the breadth of associations between obesity and cancer.

The Biological Connection Between Metabolism and Cancer

Alterations in the metabolic pathways of cancer cells and normal cells have been described and understood as part of the cancer phenotype for over 100 years. A recent acceleration in this understanding has come from novel technology that has allowed for the evaluation of hundreds of metabolites at the same time within a single experiment (metabolomics). A coherent description of the role of alterations in metabolism and cancer was recently articulated by Hanahan and Weinberg (2000). In the follow-up to their millennial description of the 'hallmarks of cancer' they describe 'metabolic reprogramming' of cancer cells as an enabling event to the previously defined hallmarks of cancer, and in so doing, provided a clear and strong connection between metabolic alterations in cancer cells and the fundamental features of carcinogenesis and the overriding cancer phenotype. These fundamental features of the cancer phenotype are shared across species, and as such it is not surprising that the associations between altered cellular metabolism and cancer are found in dogs with naturally occurring cancer.

The Warburg Effect

The Warburg Effect describes the observation that cancer cells have cellular metabolism distinct from that of normal cells, arguably representing emerging connections between cancer and metabolism. Specifically, cancer cells generate a greater amount of their energy from glycolysis, in contrast with normal cells, which follow distinct pathways for energy production in anaerobic and aerobic environments. The Warburg Effect goes further to suggest that this preference for glycolysis, is a fundamental feature of cancer and a component of carcinogenesis (Vander Heiden *et al.*, 2009; Tran *et al.*, 2016).

Metabolism of Metastasis

Other recent reports have described recurrent differences in the cellular metabolic profiles of metastatic cells compared with non-metastatic cells. Briefly, these data suggest a ‘flexibility metabolism’, which is distinct from the Warburg Effect, and can be described by an ability of metastatic cells to generate adenosine triphosphate (ATP) from a variety of distinct substrates. These findings lend themselves to an hypothesis of metastasis and cancer that states that highly metastatic cells utilize a variety of cellular programmes to overcome harsh cellular conditions experienced during the metastatic cascade. Indeed, one of these programmes is the ability to generate ATP from a variety of substrates and efficiently use this ATP to overcome stress. The connection between metastatic proclivity and metabolism has been suggested in both dog and human osteosarcoma.

The Association Between Cancer and Obesity in People

More than 1,000 epidemiological studies have examined the association between obesity and various types of cancer. Recently, the International Agency for Research on Cancer (IARC) reviewed the collective body of evidence of studies that have examined body fatness and cancer risk (Lauby-Secretan *et al.*, 2016). Most studies examined adult BMI, some also examined waist circumference (Cerhan *et al.*, 2014).

An expert panel concluded that there was sufficient evidence linking obesity with higher risk of 13 cancer types including those of the oesophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast, corpus uteri, ovary, kidney, meninges (meningioma), thyroid and plasma cells (multiple myeloma). The magnitude of associations ranged from a relative risk (of the highest BMI category versus normal BMI) from 1.1 (95% confidence interval [CI] 1.0–1.1) for thyroid cancer to 7.1 (95% CI 6.3–8.1) for cancer of the corpus uteri. Oesophageal adenocarcinoma carried a relative risk of 4.8 (95% CI 3.0–7.7), while all others ranged between 1.1 and 2.0. Limited evidence also exists for cancers of the male breast, prostate and lymphocytes (diffuse large B-cell lymphoma). Inadequate evidence existed for all other sites (Lauby-Secretan *et al.*, 2016).

Cancer Risk Association Studies in Veterinary Medicine

Although it is clear that alterations in cancer cells are conserved and similar across species, the relationship between obesity and cancer risk or progression has not been shown to be as strong in veterinary patients (most often dogs). For the most part, this can be ex-

plained by the nature and design of epidemiological studies examining lifestyle risk factors for cancer development and outcome in veterinary medicine. These risk association studies have been retrospective in design and relatively small. As such, they are unlikely to uncover associations between obesity (most often clinically characterized as body condition score) and specific cancer diagnoses. Furthermore, it is notable that the spectrum of cancer histopathology commonly seen in dogs does not include those cancers (i.e. epithelial cancers) where obesity risk associations have been defined in people. Nonetheless, the shared environment and lifestyle of pet animals and their human families has provided a strong rationale to examine lifestyle and environmental exposures as risk factors for cancer.

An example of such a risk association study includes a 1989 investigation of insecticide exposure, obesity and the risk of bladder disease in dogs. In this study, the risk of bladder cancer was highest in the obese cohorts (Glickman *et al.*, 1989). This study identified an increased and dose-dependent risk for bladder cancer in dogs living in households where lawn chemicals were used, and a higher risk in obese dogs with such exposures, potentially linked to the fat solubility of these chemical exposures. Similar concerns with bladder cancer risk and lawn chemical exposure have been made in human populations.

In a similar cancer association study, the risk of canine lymphoma was increased in dogs living in homes with proximity to high-power electrical corridors (Reif *et al.*, 1995). Again, this points to the potential comparative value of these studies in dogs; similar concerns have been expressed in human populations experiencing these environmental and occupational exposures. In this study, no association was found between obesity and lymphoma risk. It is reasonable to ask how routinely body condition scoring (a surrogate measure of obesity status) is retrievable from a retrospective medical record review.

The Value of Prospective Studies in the Dog

Based on the insights and results taken from retrospective risk association studies, the fully overlapping hallmarks of cancer in the dog and man and the shared environmental and lifestyle exposures for dogs and people, it is reasonable and likely that prospective studies of such environmental and lifestyle ‘exposures’ on cancer risk in dogs will be highly informative. Furthermore, after the identification of a risk association, the opportunity to explore the value and benefit of prevention interventions will be greatly enhanced by prospective studies in the dog. These values include the compressed progression rates of

cancer in dogs compared with people and the opportunity to collect biological specimens prospectively from dogs for the validation of biomarkers of exposure and the pharmacodynamics of markers of exposure or response to an intervention (e.g. exercise and weight loss).

The parallels in the clinical care and oversight of a prospective cohort of dogs and people will provide significant value to the conduct of such a prospective study. These values have been part of the motivation behind the first prospective cohort study in dogs. Launched by the Morris Animal Foundation, the proposed cohort includes golden retriever dogs, which are recognized for their high risk of cancer (<http://www.morrisanimalfoundation.org/>).

How Stakeholders Can Affect Risk Factors for Obesity

Over the past several decades, numerous expert bodies have made recommendations related to population or public health strategies for human obesity prevention by altering risk factors ([White House Task Force on Childhood Obesity, 2010](#); [Institute of Medicine, 2012](#)). The recommendations from these groups focus on both diet and physical activity and the promotion of a multilevel approach that supports individuals and families needs around eating better and moving more. Interventions can be deployed by multiple stakeholders from a variety of sectors. These can include counselling, education and community awareness campaigns, incentives, providing supportive organization-level offerings such as school and worksite wellness programmes and community design changes such as zoning policy that alters community design to support safe walking and biking ([Khan *et al.*, 2009](#); [Institute of Medicine, 2012](#)).

The US Preventive Services Task Force (USPSTF) recommends that all people 6 years of age and older be screened for obesity and that those with a body mass index of ≥ 30 be offered intensive, multicomponent behavioural interventions to address risk factors ([USPSFT, 2010](#); [Moyer, 2012](#)). These interventions would typically include ‘behavioural management activities such as setting weight loss goals, improving diet or nutrition and physical activity and self-monitoring’. These intervention programmes are often located within hospitals, clinics or in community venues. Thus, doctors and other healthcare providers have a key role in engaging with individuals about how excess weight can impact on their health.

Some groups have indicated that healthcare providers, in addition to their role in the clinical assessment, counselling and treatment of obesity may also

have a role in championing change within their communities (<http://obesity.nichq.org/stories/Training%20a%20New%20Generation%20of%20Advocates>). Examples include promoting safe routes to school and parks and recreation programmes within communities.

In addition, health professionals and organizations can play a variety of additional roles in bridging the clinic and community. For instance, they can connect families to community-based resources for physical activity such as trails and/or schools that have shared use agreements for after hours use. This can be done through text messages, patient portals, Apps or brochures. Healthcare providers can also ensure their waiting rooms and clinics are health promoting to reduce risk, such as by avoiding unhealthy vending and snack options for clients if any food or beverages are provided.

The One Health Perspective

Understanding the environmental, genetic and behavioural origins of diseases known to be shared across species can help us improve and expand the tools available for their prevention and management ([Rijnberk *et al.*, 2003](#)). This is a goal of the One Health initiative, a movement to forge equal, inclusive collaborations between practitioners and researchers working in human and veterinary healthcare.

The prevalence of, and risk factors for, pet and human obesity have been well described. The complex obesity landscape shares attributes of a ‘wicked’ problem ([Ackoff, 1974](#)), in that there is no prescribed way forward, it involves multiple stakeholders with different perspectives and there is no ‘right’ or ‘optimal’ solution for every family or every community; wicked problems cannot be solved with known methods. A One Health lens on the obesity crisis can spur innovative and novel approaches by bringing together engaged groups of people to take meaningful roles in supporting individuals in promoting their health and the health of their animal companions, and to support community offerings for eating better and moving more.

Cross-species data will be critical to moving towards these goals, yet such data are currently sparse. Prospective studies might further explore the associations between obesity and feline diabetes mellitus or canine cancer. One relatively easy step towards developing data for research could be to add as few as one to three questions about pet companionship and pet health to ongoing, nationally representative datasets on human health. Another step could be to develop a number of primary data collection sites, with sampling at pet adoption centres or veterinary clinics, where people and their animal

companions could be recruited, basic health information collected, and then followed over time. New data collection such as this would allow us to move beyond parallel descriptions and add information on how the health of people and animals living together is correlated and how health can be improved in both simultaneously.

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Conflict of Interest Statement

The authors declare no conflicts of interest with respect to the publication of this manuscript.

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