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An open science study of ageing in companion dogs

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Abstract

The Dog Aging Project is a long-term longitudinal study of ageing in tens of thousands of companion dogs. The domestic dog is among the most variable mammal species in terms of morphology, behaviour, risk of age-related disease and life expectancy. Given that dogs share the human environment and have a sophisticated healthcare system but are much shorter-lived than people, they offer a unique opportunity to identify the genetic, environmental and lifestyle factors associated with healthy lifespan. To take advantage of this opportunity, the Dog Aging Project will collect extensive survey data, environmental information, electronic veterinary medical records, genome-wide sequence information, clinicopathology and molecular phenotypes derived from blood cells, plasma and faecal samples. Here, we describe the specific goals and design of the Dog Aging Project and discuss the potential for this open-data, community science study to greatly enhance understanding of ageing in a genetically variable, socially relevant species living in a complex environment.

Age is the strongest risk factor for most major causes of death and disability in developed nations[1]. Although many aspects of ageing are shared across all individuals, the rate and order of various forms of functional decline and onset of disease vary greatly[2,3]. The mechanisms underlying individual trajectories of ageing are influenced by complex combinations of genes, environment and lifestyle that remain poorly understood. Most of what we know about the biology of ageing comes from laboratory studies of inbred, laboratory-adapted species, including yeast, worms, flies and mice. While these laboratory

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models have facilitated rapid progress in identifying evolutionarily conserved mechanisms of ageing, we cannot be certain of the extent to which these findings reflect causal determinants of ageing in outbred populations in heterogeneous environments. To better understand how genes and environment shape ageing in non-human animals outside the laboratory and to generate knowledge that could readily translate to human ageing, we have turned to the companion dog as a powerful animal model that shares the human environment but ages more rapidly. Here, we describe the Dog Aging Project (DAP)[4], an open-data long-term longitudinal study of ageing in tens of thousands of companion dogs. The scientific objectives of this study are to identify the genetic, environmental and lifestyle factors that influence ageing in dogs, to discover the underlying molecular mechanisms by which they do so and to test potential ways to increase the duration of healthy lifespan in dogs.

We have designed the DAP to achieve our overarching scientific goals (Box 1) while also ensuring the well-being of all study participants, complying with all appropriate regulations, meeting the highest ethical standards and creating an open-data platform. The DAP is an interdisciplinary, open-data, community science project that consists of a team of more than 100 staff, students, faculty and veterinarians from more than 20 academic institutions, along with over 30,000 canine participants and their owners (https://dogagingproject.org). Together, we are creating an enormous resource of health, behavioural and lifestyle data gathered from owners and veterinarians, complemented with detailed molecular and environmental profiling. The DAP includes observational studies, combining both retrospective cross-sectional and prospective longitudinal data, as well as a randomized, placebo-controlled clinical trial for healthy ageing. Data and biospecimens will be collected annually and made available as a public resource. Moreover, the study is designed in a way such that independent researchers can create integrated ancillary studies to benefit from the powerful DAP infrastructure.

The companion dog is an ideal animal in which to study biological ageing. Dogs are one of the most variable animal species known in size, shape and behaviour[5]. Moreover, like humans, individuals vary in life expectancy and the spectrum of diseases they are likely to encounter. Companion dogs experience nearly every functional decline and disease of ageing that people do, and, importantly, these diseases are diagnosed and treated within a sophisticated healthcare system that parallels human healthcare in many ways. Companion dogs age approximately seven to ten times faster than humans, allowing for longitudinal and interventional study in the timeframe of just a few years. They also share the human physical and chemical environment, a major determinant of ageing that cannot be adequately modelled in laboratory studies. For all of these reasons, findings from ageing companion dogs could readily translate to human ageing[6]. Finally and perhaps most importantly, companion dogs are considered as family by hundreds of millions of people around the world. Simply put, people love dogs. This deep commitment allows the DAP to engage the general public in science in a way that few research projects can and enables the project to collect detailed, nuanced information about each participant dog's unique life experiences in a way that cannot be duplicated in any other species. This relationship, unparalleled in other animal models, provides intrinsic value to the research beyond what is learned about human ageing.

Design of the DAP

The power of the DAP lies in our ability to capture the breadth of diversity of companion dogs and to collect a rich array of data about each dog. The greater the diversity, the greater the opportunity to characterize the age trajectory of diseases, to identify biomarkers and to discover genetic and environmental risk factors for disease outcomes. The target study population consists of dogs of all breeds (both purebred and mixed breed), ages, sizes and sexes (males and females, intact and sterilized).

Structurally, the DAP can be considered as five overlapping cohorts or groups of dogs (Fig. 1a). The largest group is the DAP Pack, which consists of all dogs whose owners successfully complete the Health and Life Experience Survey (HLES) (described below). Once enrolled, dogs are members of the Pack for the dog's lifetime, unless the owner chooses to withdraw. Following submission of a qualifying electronic veterinary medical record, dogs in the Pack become eligible for the other, more deeply studied cohorts in which owners are sent kits for biospecimen collection. The sampled cohorts include Foundation, Precision and TRIAD (Test of Rapamycin In Ageing Dogs), as well as a cross-sectional sample of extremely old 'Centenarian' dogs, whose ages will be validated by review of medical records, which must be continuous from the juvenile period of each dog's life. Currently, participation in the DAP is open to all geographical regions in the USA (Fig. 1b). Although participation is currently limited to one dog per household, there is no limit to the total number of dogs that can join the DAP Pack. The size-stratified age distributions of dogs in the DAP Pack as of December 2020 (DAP data release 1.0) are shown in Fig. 1c.

The DAP has four primary scientific aims. These include (1) characterizing ageing in companion dogs on three separate axes: multimorbidity, frailty and inflammageing; (2) using low-coverage whole-genome sequencing with imputation on at least 10,000 dogs to analyse the genetic architecture of age-related traits in dogs; (3) collecting metabolome, epigenome and microbiome profiles to develop biomarkers of ageing in dogs and to better understand the mechanisms by which genetic, environmental and lifestyle variation influence ageing; and (4) carrying out a randomized, double-masked, placebo-controlled study to determine the effects of rapamycin on lifespan and healthspan in large-breed, middle-aged dogs.

Informed consent and cohort assignment

Dog owners are recruited through mainstream media, social media and word of mouth, and they nominate their dogs through the DAP website. They are then invited to create their own personal password-protected online portals, through which they can share information about their dogs. DAP participant data are collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools[7,8] hosted in Microsoft's Azure cloud platform. The DAP's Research Study Participant Privacy Policy (https://dogagingproject.org/privacy-policy/) outlines the project's commitment to safeguarding human participants' data, including any personally identifiable information collected by the study. Owners are led through an informed consent process to ensure that they understand the purpose of the study, the requirements for participation, the potential risks and benefits for both them and their dogs, their rights and the methods used to maintain

confidentiality. Owners are given multiple opportunities to ask questions before digitally indicating consent. Once consent is obtained, owners are requested to complete the HLES and are then enrolled in the DAP Pack. There are additional informed consent processes for dogs selected to participate in each of the sampled cohorts.

To achieve our scientific objectives, the DAP needs to recruit and retain a very large and committed group of participating owners and must also provide guidance to their primary care veterinarians (Fig. 2). As this is a community science project and all study subjects are privately owned dogs, we have created robust platforms that allow us to communicate with, educate and engage owners, with the goal of maximizing recruitment and retention. We produce a monthly digital newsletter, currently received by over 85,000 people, which explains our research goals and methods in lay language and regularly engages owners in surveys that maintain their interest. We communicate with the public through regular DAP blog posts and conventional social media platforms, and we have launched a private social media community, the Dog Park, to build retention through continuous engagement with Pack members. A dynamic FAQ system enables participants to resolve many of their own questions quickly, although our direct helpdesk remains an essential feature to support our project, with almost 20,000 resolved enquiries in 2020.

Dogs are chosen for the sampled cohorts from Pack members whose owners have submitted qualifying electronic veterinary medical records. While it is possible that this requirement creates a bias in the sampled cohorts towards dogs who receive regular veterinary care, participant access to regular care may also support our goal of studying dogs across the ageing trajectory. Strata were carefully designed in advance for each cohort to ensure diversity in dog size, sex, age at enrolment, breed background (pure or mixed) and geographical location. Eligible dogs are randomly sampled within these strata and invited to these additional cohorts until targets are met. The additional requirements for each cohort are explained to the owners, and they are invited to ask questions before providing informed consent. Once dogs are enrolled in these sampled cohorts, the specific biospecimens that are collected depend on the cohort to which the dog is assigned.

Data collection

All data types collected are summarized in Table 1. The primary survey instrument used to collect information about members of the DAP Pack is the HLES. At the time of enrolment in the Pack, owners are asked to provide extensive information about their dogs, including their behaviour, diet, use of medications and preventatives, physical activity, indoor and outdoor environments and comprehensive health history. The initial HLES data are considered as that dog's baseline data, regardless of the dog's age at the time of enrolment. Owners are asked to update the HLES annually, for the lifetime of the dog, to identify changes in the dog's environment, behaviour, activity and medication, as well as their overall health status and any specific diagnoses made within the previous year. Importantly, when they report their dogs' ages, owners are asked how certain they are of age, as well as their source of age information. Certain demographic and health information from the HLES, including age, will be confirmed by data extraction from submitted electronic veterinary medical records. Pack members are subsequently provided additional surveys

designed to assess, for example, canine cognitive function, the dog–owner relationship and the end-of-life experience, as well as specific tasks to measure morphology, mobility and more. The existence of the Pack and private online portals for all users makes it simple and efficient to launch new surveys as relevant topics arise.

For dogs in any of the sampled cohorts, each owner is mailed a kit with a cheek swab for DNA collection, including printed instructions and a link to online video instructions. Owners return the kits directly to the sequencing facility for low-pass-coverage whole-genome sequencing[9].

Owners of dogs enrolled in the Precision cohort receive biospecimen kits annually. The biospecimens are collected by each dog's primary care veterinarian. Each TRIAD cohort dog receives a similar kit biannually. Owners of TRIAD dogs bring their dogs to one of seven US veterinary teaching hospitals every six months, where the samples are collected and the dog's cardiac health and function are also assessed.

Biospecimen kits include vials for collection of whole blood, plasma, serum, urine, hair and faeces as well as dried blood spot cards (Table 1). These kits are shipped to a commercial veterinary reference laboratory, where routine clinicopathologic assays are performed immediately. Biospecimens are then forwarded to DAP laboratories for analysis of metabolome, microbiome, epigenome and flow cytometry profiles, as well as inflammageing assays[10]. Residual biospecimens are sent to the DAP Biobank, housed at the Cornell Veterinary Biobank, and made available for analysis by the research community (Fig. 3a).

We have determined quality requirements for biospecimens based on their intended purposes (for example, genotyping, sequencing and metabolomic analysis), and we have conducted pilot studies to identify the amount of tolerable variation in biospecimen collection, transport and handling. For all biospecimens collected, we therefore document pre- and post-analytical quality data such as collection time, transportation conditions, quality control results[11,12] and quality assurance data, such as equipment calibration records and reagent lot numbers[13]. For survey and electronic medical records data, we have established and extensively piloted protocols that ensure ease of data collection, storage and analysis, and we have tested for reproducibility of survey data within individual participants. Finally, for all analyses, we have created reproducible computational pipelines with associated quality assurance metrics, including detailed annotations and software versions.

Data from surveys and biospecimens are complemented with extensive environmental data. In addition to information about the home environment provided by the owner through the HLES, the DAP also uses secondary data sources to compile information about each dog's external environment, based on the owner's address. These secondary measures include (1) tract-level sociodemographic and economic neighbourhood variables from the American Community Survey[14]; (2) tract-level air pollution variables (four gases: O_3, CO, SO_2, NO_2; two aerosols: PM_{10}, $PM_{2.5}$) from the Center for Air, Climate and Energy Solutions[15]; (3) county-level temperature and precipitation measures from the National Oceanic and Atmospheric Association[16]; and (4) neighbourhood walkability as

characterized by Walkscore and tract-level residential density[17] (Fig. 3b). These data are attached to the geocodes related to the primary and secondary addresses to characterize each dog's external environment.

Team management

The key elements to effective DAP study management include a well-defined organizational structure, clear policies and procedures, effective lines of communication and a culture that encourages and supports multidisciplinary collaboration. DAP functional and operational cores support the scientific goals of internal investigators and external collaborators. Standing committees and temporary working groups are established on an as-needed basis to tackle recurring or short-term needs across the programme. A scientific advisory board and an animal welfare advisory board provide independent expert advice and guidance to the executive operations team, and a National Institute on Aging-constituted data and safety monitoring board oversees the TRIAD trial.

Ethical, legal and social implications

The DAP has many features in common with contemporary human subjects research such as data collection, interpretation and sharing. Although the depth of the human–animal bond may resemble a parent–child relationship, the nature of these relationships also differs in important ways (that is, animals are legal property and owners give permission to use their dogs) that have ethical and legal implications for research on pets. Veterinary and animal ethical concerns about using pets as research subjects include non-uniform oversight protection and the need to respect research subjects who cannot consent to participation. The clinical trial arm of the DAP (TRIAD) requires additional consideration about the ethics of testing therapeutic interventions in healthy subjects[18,19]. The DAP study team carefully considers how to best ensure the safety of our canine participants and how to best support the human–dog bond. The general approach we take to dog owner informed consent for their dog's participation is modelled after informed consent used for human subjects research. In addition to the independent animal welfare advisory board, which is led by a veterinary bioethicist, the DAP team includes a paediatric bioethicist as a co-investigator and a regulatory manager with human subjects protection expertise. The bioethicists and the regulatory manager provide regular guidance to DAP leadership. Efforts are already underway to take advantage of the valuable opportunities for DAP-related research to specifically investigate the ethical, legal and social implications of research on ageing in dogs.

Key outcomes

Scientific findings

- We anticipate important outcomes in each of our scientific aims over the next few years.
- While human studies have clear metrics for healthy ageing, including age-related changes in clinicopathological values and frailty and morbidity indices, among

others, relatively little is known about what constitutes normative ageing in dogs. Our data will give veterinarians and scientists the tools to assess how well a specific dog is ageing and set the stage for studies on the determinants of normative ageing. The DAP has already begun collecting and analysing the data that lay the groundwork for canine-specific gerontology.

- Whole-genome sequencing data will enable us to identify genetic variants, environmental and lifestyle factors, and their interactions that are associated with diverse measures of ageing. We are on track to complete sequencing of the genomes of 10,000 dogs by the end of 2022.
- We will create a systems biology model of ageing in dogs, through annual measures of the metabolome, microbiome and epigenome of Precision and TRIAD dogs. Processing of the first year of omic samples for Precision and TRIAD dog samples will be completed during 2022. We expect that these data will generate predictive and prognostic biomarkers of ageing and will point to causal factors that explain the mechanisms by which specific genetic or environmental factors influence ageing. Importantly, candidate predictive biomarkers of ageing will be able to be validated against true lifespan in a shorter period of time than would be possible in any human cohort.
- We will test the hypothesis that a one-year course of weekly low-dose rapamycin can increase lifespan, improve heart and cognitive function, and reduce age-related disease incidence in middle-aged, large-breed dogs. Enrolment into TRIAD began in June 2021 and will continue through 2022. This clinical trial is noteworthy as a test of a geroprotective drug with lifespan and healthspan metrics as endpoints, given that it will occur in a species outside of a laboratory.

Data and sample release

In addition to our primary scientific aims, the DAP is an open science project with a central goal of sharing not just results, but also raw data and biospecimens, with the research community. All de-identified DAP study data, including participant surveys, analysis of biospecimens, environment data and information extracted from electronic veterinary medical records, are made available on DAP's research data repository, which is housed on the Terra platform (http://app.terra.bio) run by the Broad Institute of MIT and Harvard, with the first public release scheduled for the first quarter of 2022. The Terra platform will facilitate open science and data sharing, can serve as a one-stop data and code repository and provides direct access to Google's high-performance and shareable computing environment[20]. Access to Terra will be provided to users once they sign the DAP data use agreement (available at https://pubs.dogagingproject.org), and access does not require collaboration with DAP researchers.

From each processed biospecimen kit, a subset of biospecimens will be stored in the DAP Biobank. These biospecimens will be made available to qualified researchers, as long as the proposed research is in the public interest and the researchers commit to providing the DAP with any data obtained from sample analysis for potential addition to the DAP data repository.

Our goal is that the DAP continues indefinitely, with the infrastructure that we have created serving as a foundation on which other studies can be built, including studies that are ancillary to the current focal cohorts, as well as future studies that we have not yet envisioned based on new or existing cohorts. Thus, the DAP makes available to the research community not only the data that it collects, but also its research infrastructure, which will enable future research initiatives to examine new hypotheses and technologies.

Interdisciplinary research

The DAP's primary goal is to generate and facilitate discoveries on the fundamental biology of ageing, but the impact of the DAP will go far beyond this goal. The data collected will provide research opportunities not only for those working on the biology of ageing, but also for epidemiologists, geographers, ethicists, veterinarians and others studying diverse clinical and basic research questions. The DAP also creates a unique platform for educational opportunities on a topic with broad appeal to students from diverse backgrounds: the health and longevity of our pet dogs. Because not all potential users may have the computational expertise to access our open science platform, the DAP will develop user-friendly data access platforms to support enquiry by science, technology, engineering and mathematics (STEM) educators and their students, from kindergarten to 12th grade through college.

Conclusion

The DAP is an ambitious research initiative, creating a resource with the power to transform veterinary medicine, ageing research and many scientific and non-scientific fields of enquiry. Similar to all longitudinal studies, the success of the DAP depends in large part on strong and enduring relationships with many stakeholders, including participating dog owners, veterinarians and researchers. To accomplish this, we have devoted considerable resources to building strong, diverse communication pipelines; actively engaging with participants, veterinarians and scientists; and providing open access to the wealth of data produced by this project. We are also putting great effort into participant retention, and we are redoubling our efforts to capture the diverse dimensions of US dog owners who are not yet adequately represented in our study population. Through these efforts, the DAP is establishing the foundation for an innovative community science approach to ageing research in dogs. We are excited to use the DAP as a platform on which to build a truly transformative, interdisciplinary and integrated research programme.

Data availability

The data used to generate Fig. 1b, c are freely available for download at https://data.dogagingproject.org.

Acknowledgements

All dog research described here, including informed owner consent, is approved by the Texas A&M University Institutional Animal Care and Use Committee, under AUPs 2018-0401 CAM and 2018-0368 CAM. The DAP is supported by grant U19AG057377 from the National Institute on Aging, a part of the National Institutes of Health, and by private donations. We thank S. Moon for help in preparing figures.

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Box 1

Goals of the DAP

Objectives—science of ageing

- Define normative ageing in dogs as a function of breed, size and sex
- Identify genetic and environmental determinants of age-specific morbidity and mortality in companion dogs
- Develop panels of prognostic and predictive biomarkers
- Increase the duration of healthy lifespan in dogs Objectives—open science
- Create an open-data resource for comprehensive study of the genetic and environmental determinants of healthy ageing in companion dogs
- Provide researchers with access to biospecimens through the DAP Biobank, together with the detailed longitudinal data associated with each biospecimen
- Build and maintain a research infrastructure that allows for addition of new studies within the DAP framework
- Study and promote ethical approaches for research in companion animals

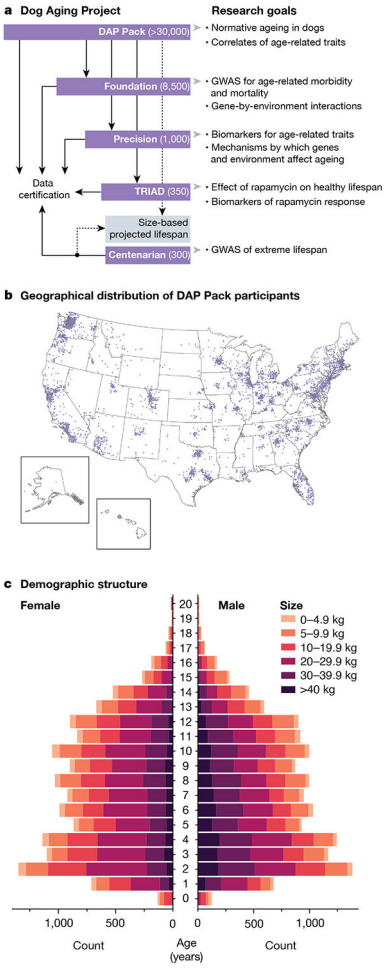

Fig. 1 |. Structure of the DAP cohorts.

a, Dogs become members of the DAP Pack once owners complete the HLES. From the Pack, a size-, age-, sex- and location-balanced population of dogs is selected to join each of the sample collection cohorts (Foundation, Precision and TRIAD). Dogs may be selected to join the Centenarian cohort (dogs in the top 0.1% of their size-specific age distribution) through the Pack or through independent outreach. Data and samples collected from each cohort are tailored to address specific research goals. **b**, DAP Pack members have enrolled from all 50 US states. On this map, one dot represents five participants, and dots within a given county are randomly placed. **c**, Age distribution of DAP Pack members, stratified by size: 0–4.9 kg, 5.0–9.9 kg, 10.0–19.9 kg, 20.0–29.9 kg, 30.0–39.9 kg and ≥40.0 kg.

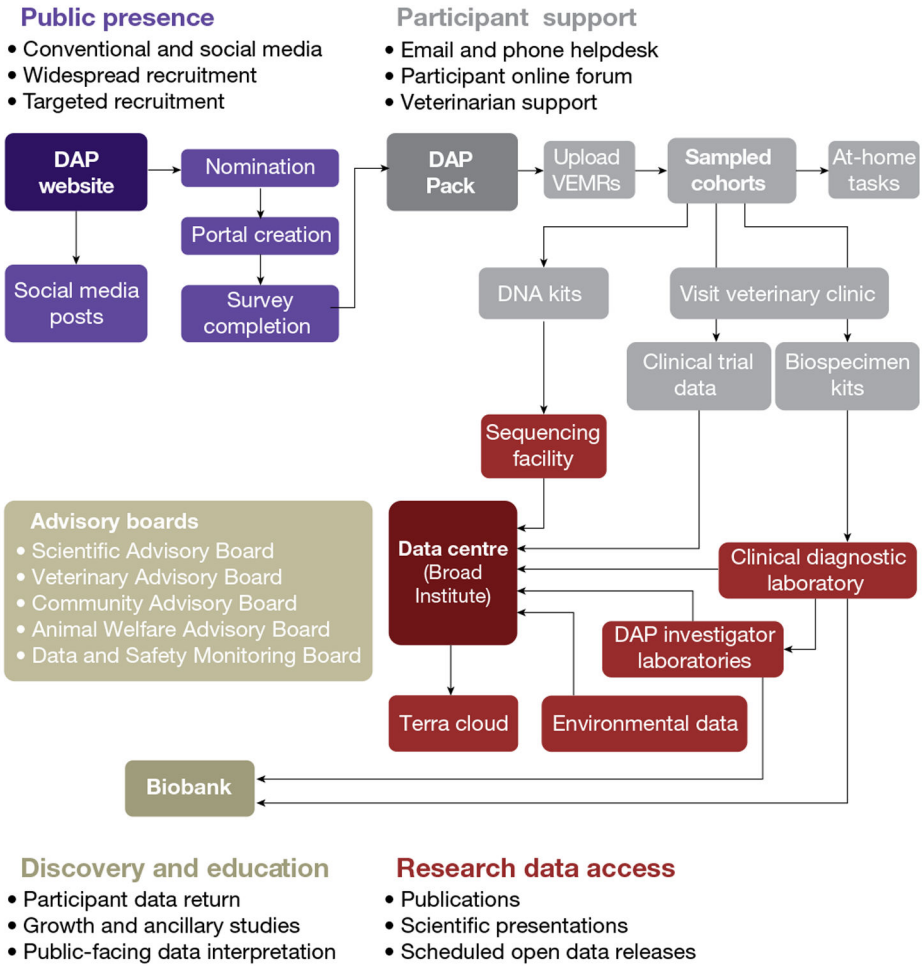

Fig. 2 | DAP integration.

Information flow through the DAP begins when an owner signs up to participate with their dog on the DAP website (upper left). Owner information and survey data flow through the DAP customized REDCap platform. After completing the HLES, participants join the DAP Pack. DAP Pack members whose owners upload qualifying veterinary electronic medical records (VEMRs) are eligible for all other nested cohorts, including those from which samples are collected. Deep and broad participant support is made available at every step to promote adherence to study protocols. Samples flow from owners, primary care veterinarians and participating veterinary teaching hospitals to the sequencing facility or the Texas A&M Veterinary Medical Diagnostic Laboratory and, from there, to DAP investigator laboratories and the Biobank. Guidance and monitoring are provided by advisory boards and volunteers. As an Open Science study, the DAP provides curated, de-identified raw data to the research community through the data centre, and shares discoveries and results with DAP participants to promote retention. The DAP cohorts will also serve as the foundation for ancillary studies by DAP team members and the broader research community.

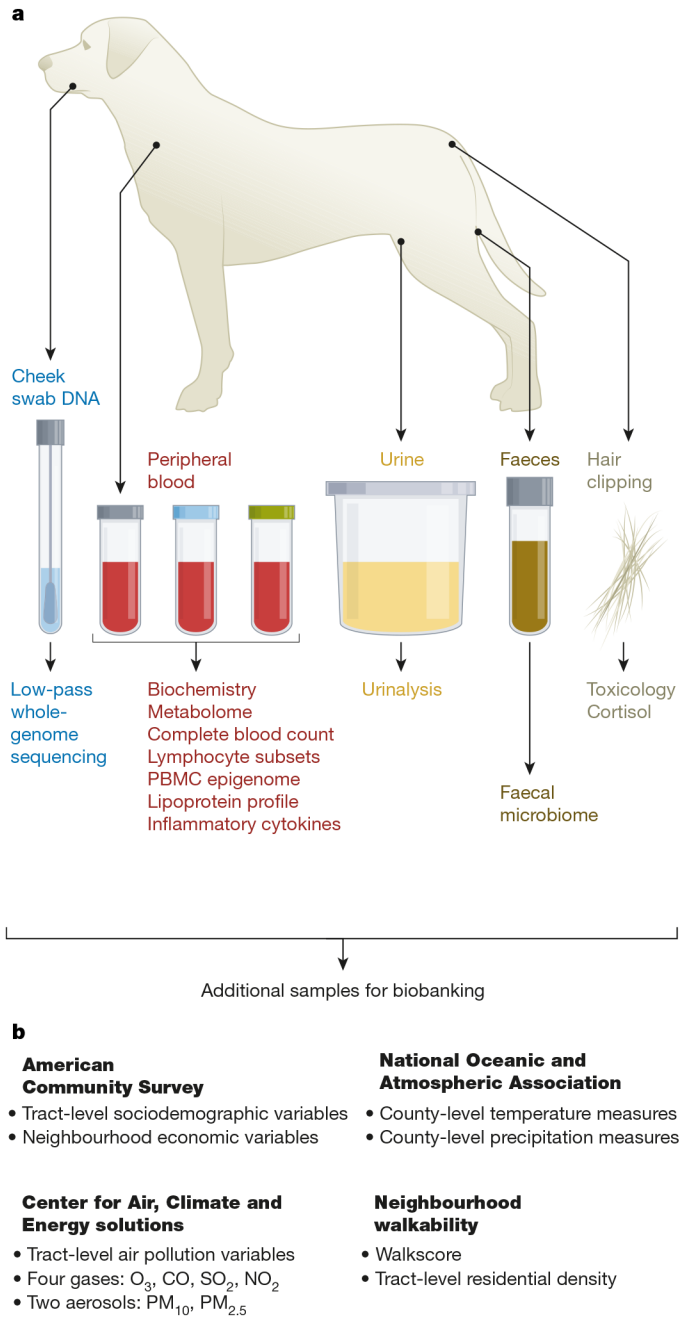

Fig. 3 |. Biospecimen and environmental measures.

a, Dogs in all sampled cohorts provide a cheek swab for low-pass whole-genome sequencing (n = 10,000). From each dog enrolled in the Precision cohort (n = 1,000) or TRIAD cohort (n = 350), veterinarians will collect peripheral blood, urine, faeces and hair and ship these samples to the DAP team for immediate processing or storage in the DAP Biobank. **b**, Environmental data are collected from publicly available sources and associated with each participant, based on the primary address of the dog. All biological and environmental data will be stored in the DAP data repository and made publicly available.

Table 1|

Current and planned data

Data source	Cohorts included	Explanation
Owner-reported surveys and measures		
Health and Life Experience Survey (HLES)	All	Comprehensive annual information about each dog's behaviour, diet, use of medications and preventatives, physical activity, indoor and outdoor environments and health history
Canine Social and Learned Behavior Survey (CSLB)	All	Information about cognitive awareness and at-home human–dog interactions, using a previously validated instrument[21]
End-of-Life Survey (EOLS)	Enrolled dogs who die	Owner-reported cause of death, observed changes associated with ageing or illness, perimortem veterinary care, quality-of-life assessment and reasons for euthanasia (if performed)
Morphometrics and mobility (M&M)	F, P, T (Pack in future)	At-home measurements of dog height, face shape, body length, limb length, thigh circumference, speed on a flat surface and speed running up the stairs (if safe and feasible)
Cognitive task performance	F, P, T (Pack in future)	At-home performance on a series of standardized behavioural tests assessing short-term memory
Veterinary data		
Veterinary electronic medical records	All are invited	Tiered extraction of data including veterinarian-recorded age, sex, breed and weight, date of spay/castration (if performed), frequency of veterinary visits, vaccination history, other preventive care history and anaesthetized procedures
Canine Multimorbidity Index	F, P, T (Pack in future)	Weighted scoring system for veterinarian-reported presence or absence of 16 specific chronic conditions
Biological and physical data		
Cheek swab	F, P, T	Low-pass whole-genome sequencing
Biospecimen kit	P, T	Complete blood count, chemistry profile, urinalysis, lymphocyte subsets, inflammatory cytokines, lipoprotein profile, epigenome, plasma metabolome, faecal microbiome
Activity monitors	P, T	Three-axis accelerometers on dog collars
Cardiology examination	T	Cardiac physical exam, echocardiogram, electrocardiogram, blood pressure measurement
Banked samples	P, T	EDTA whole blood, DNA, PBMCs, serum, plasma, hair, dried blood spot cards
Environmental data		
Geospatial data	All	Sociodemographic and economic neighbourhood characteristics, air pollution (O_3, CO, SO_2, NO_2; two aerosols: PM_{10}, $PM_{2.5}$), county-level temperature and precipitation measures, and neighbourhood walkability

F, Foundation; P, Precision; T, TRIAD; PBMCs, peripheral blood mononuclear cells.