Published in final edited form as:

Eur Radiol. 2016 January ; 26(1): 15–24. doi:10.1007/s00330-015-3796-y.

Normal Thymus in Adults: Appearance on CT and Associations with Age, Sex, BMI and Smoking

Tetsuro Araki, M.D.^{1,2}, Mizuki Nishino, M.D.¹, Wei Gao, M.S.³, Josée Dupuis, Ph.D.^{3,4}, Gary M. Hunninghake, M.D., M.P.H.⁵, Takamichi Murakami, M.D., Ph.D.², George R. Washko, M.D.⁵, George T. O'Connor, M.D.^{4,6}, and Hiroto Hatabu, M.D., Ph.D.¹

¹ Department of Radiology, Center for Pulmonary Functional Imaging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

² Department of Radiology, Kinki University Faculty of Medicine, Osaka-Sayama, Japan

³ Department of Biostatistics, Boston University School of Public Health, Boston, MA

⁴ The National Heart Lung and Blood Institute's Framingham Heart Study, Framingham, MA

⁵ The Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

⁶ Pulmonary Center and Department of Medicine, Boston University School of Medicine, Boston, MA

Abstract

Objective—To investigate the CT appearance and size of the thymus in associations with characteristics of participants.

Materials and Methods—2540 supposedly healthy participants (mean age 58.9 years, 51% female) were evaluated for the CT appearance of thymic glands with four-point scores (according to the ratio of fat and soft tissue), size, and morphology. These were correlated with participants' age, sex, BMI, and smoking history.

Results—Of 2540 participants, 1869 (74%) showed complete fatty replacement of the thymus (Score 0), 463 (18%) predominantly fatty attenuation (Score 1), 172 (7%) half fatty and half soft-tissue attenuation (Score 2), and 36 (1%) solid thymic gland with predominantly soft-tissue attenuation (Score 3). Female participants showed less fatty degeneration of the thymus with higher thymic scores within age 40–69 ($P < 0.001$). Participants with lower thymic scores showed higher BMI ($P < 0.001$) and were more likely to be former smokers ($P < 0.001$) with higher pack-years ($P = 0.04$).

Conclusions—Visual assessment with four-point thymic scores revealed a sex difference in the fatty degeneration of the thymus with age. Women show significantly higher thymic scores than men, suggesting less fat content of the thymus, during age 40–69. Cigarette smoking and high BMI are associated with advanced fatty replacement of the thymus.

Keywords

Computed tomography; Thymus Gland; Adult; Body Mass Index; Smoking

INTRODUCTION

The thymus demonstrates a unique morphological change over time in its size, shape, and density according to age. The thymic gland reaches its maximum size at puberty and eventually undergoes “involution”, a gradual decrease in size with replacement of fatty tissues [1, 2]. Therefore, normal appearance and size of the thymus have been elusive. In the 1980s, investigations of the thymus on CT were conducted by Barron et al [3] and Francis et al [4] with a relatively small number of subjects. Thereafter, advancing technology and modern CT scanners have significantly improved the depiction and characterization of the thymus, which subsequently requires updates for assessment of the normal thymus. In 2012, Simanovsky et al investigated the thymus of 194 trauma patients and revealed a correlation between thymic density and age [5]. More recently, Ackman et al reported the sex differences in the thymus of 238 young patients (mostly traumatic) in their 20s; the female thymus exhibits higher CT attenuation and, more commonly, a quadrilateral configuration [6]. In the lung cancer screening study with CT scans, anterior mediastinal masses were detected in 0.4% of smokers over the age of 40 [7, 8]. A recent study revealed that the prevalence of anterior mediastinal masses was 0.9% in the population of the Framingham Heart Study [9]. Recognition of a normal thymus in adults is becoming significantly important because it can be misdiagnosed as an anterior mediastinal lesion on screening CT scans, usually performed in middle aged and older patients [5, 7]. However, there are no established guidelines for the CT characteristics of the normal thymus.

The Framingham Heart Study (FHS) originally began in 1948 to investigate epidemiologic risk factors of cardiovascular disease [10]. The original cohort was recruited independently from health condition of the participants. Subsequently, the offspring cohort, formed by children of the original cohort members and their spouses, was recruited in 1971, followed in 2002 by the third generation cohort, consisting of grandchildren from the original cohort members. Chest CT scans were performed on the offspring and third generation cohorts without any clinical intention. Investigating this large population based cohort for the thymus is distinctive from the previous studies and advantageous in defining the normal thymus.

Other than age and sex, we hypothesize that physical features (body mass index, BMI) and cigarette smoking might be associated with the appearance of the normal thymus, which have not been investigated previously. The amount of fat tissue in the anterior mediastinum is probably associated with BMI and could affect the appearance of the thymus, and there is a known suppressive effect of cigarette smoking on the immune system [11]. This knowledge helps to define the normal thymus and differentiate it from thymic lesions.

The purpose of the present study is to investigate the appearance and size of the normal thymus in the FHS cohort including middle aged and older adults, and to investigate their associations with demographic features, including age, sex, BMI, and smoking status.

MATERIALS AND METHODS

Study population

The institutional review boards at both Brigham and Women's Hospital and Boston University approved the present study and written informed consent was obtained from all participants upon enrollment in the FHS study. From the FHS participants of the offspring and third generation cohorts, eligible adult participants were enrolled for chest CT exam. Women who were pregnant or breastfeeding within 6 months were ineligible for the study. From 2008 to 2011, 2764 participants underwent chest CT scans without administration of contrast media in the supine position using a 64-detector-row CT scanner (Discovery, GE Healthcare, Waukesha, WI) with 120 kV, 300-350 mA, gantry rotation time of 0.35 seconds, and slice thickness of 0.63 mm. Of these, 131 were missing CT images, 62 had prior sternotomy, and 31 had an anterior mediastinal mass or multiple lymphadenopathy; they were excluded from the study. Therefore, 1296 women (mean age, 60.6 years; standard deviation [SD], 11.4; range 39 to 92) and 1244 men (mean age, 57.1 years; SD, 12.2; range 34 to 90), for a total of 2540 participants (mean age, 58.9 years; SD, 11.9; range, 34 to 92) were investigated for thymic appearance on CT and its association with characteristics of participants.

Evaluation of Chest CT images

Chest CT scans were evaluated for the appearance and size of the thymic glands in a fixed mediastinal window setting (WL=50 HU, WW=350 HU) on a Picture Archiving and Communication System (PACS) workstation (Virtual Place Raijin, AZE Ltd., Tokyo, Japan). Assessment of the thymus was divided into two steps: visual thymic scoring and quantitative measurements. In the first step, the thymic scoring system with a four-point scale (0-3) described previously by Ackman et al was used [6]. Each score is defined as follows: Score 0, complete fatty replacement and no identifiable soft tissue density in the thymic bed; Score 1, predominantly fatty thymus; Score 2, approximately one half fatty and one half soft-tissue attenuated thymus; Score 3, predominantly soft-tissue attenuated thymus [6] (Figure 1).

As a preliminary study to assess the validity of the thymic scoring system, two board-certified radiologists (T.A. and H.H.) reviewed 100 CT scans selected randomly from 2540 participants for intra- and inter-observer agreements. The first radiologist scored the 100 cases twice and the second radiologist did once. The two review sessions by the first radiologist were approximately one month apart. All cases were presented in a random order for each session and in a blinded manner of participants' information and other reader's or previous scores.

One of the two radiologists (T.A.) with expertise in thoracic imaging and prior experience in assessing and measuring thymic glands [12, 13] reviewed all the chest CT scans and provided a score of 0, 1, 2, or 3 for each case. In the second step of evaluations on the cases provided with Scores 1, 2, and 3, the radiologist (T.A.) used a caliper-type measurement tool on the PACS to evaluate the quantitative features of the thymus, including CT attenuation and size (anteroposterior and transverse diameters, length and thickness of each lobe) [12, 13] (Figure 2). For consistency of thymic measurements, a transaxial CT image

demonstrating the maximum anteroposterior (AP) diameter of the thymic gland was selected first and all the measurements and evaluations were made on the same image [12]. CT attenuation was measured by placing an oval region of interest (ROI) covering the maximum area of the thymic gland with soft-tissue density excluding the surrounding mediastinal fat tissue as much as possible [12, 13]. The morphology of the thymic gland was also determined using the following categories: 1) Pyramidal with convex margin, 2) Pyramidal with straight margin, 3) Pyramidal with concave margin, 4) Round or oval, 5) Irregular [13]. If the thymus varied in morphology between the lobes [5], (eg, convex margin in the left lobe and concave margin in the right), description of the dominant lobe with larger length and thickness was adopted [6].

Characteristics of participants

The characteristics of the participants, including age, sex, BMI, smoking status, and pack-year (p-y) were provided at the exam closest to the CT exam date and compared to the results of visual thymic scoring. Participant's age was categorized into six groups: age 39 or younger, 40-49, 50-59, 60-69, 70-79, and 80 or older. Thymic scores and measurement results were analyzed overall and in each age group.

Statistical analysis

Intra- and inter-observer agreements of thymic scores were indicated with the weighted Cohen κ values calculated using MedCalc (version 14.8.1, MedCalc Software, Ostend, Belgium), classified as follows: poor, $\kappa = 0-0.20$; fair, $\kappa = 0.21-0.40$; moderate, $\kappa = 0.41-0.60$; good, $\kappa = 0.61-0.80$; excellent, $\kappa = 0.81-1$ [14, 15].

All the other statistical analyses were performed using R (version 3.1.1, The R Foundation for Statistical Computing, Vienna, Austria). Participants' demographics were compared between the groups with different thymic scores by linear mixed effect models for quantitative data (age, BMI, pack-year) and generalized estimating equations for categorical data (sex and smoking status) to account for familial correlations among the FHS participants [16]. The results for BMI, smoking status, and pack-year were adjusted for age and sex. In addition, the results for BMI and pack-year were also adjusted for pack-year and BMI, respectively. The differences in thymic score between female and male, overall or in each age group, were assessed by generalized estimating equations. Correlations between quantitative measurement result (thymic size and CT attenuations) and age were assessed for female and male separately by the Pearson correlation coefficient and significance assessed using linear mixed effect models. The differences of the measurement results between female and male were assessed by the Wald test from regression estimates obtained from linear mixed effect models. P values were two-sided and regarded as statistically significant at the level of 0.05.

RESULTS

Intra- and inter-observer agreements of thymic scores were excellent; the weighted Cohen κ values were 0.87 (95% CI: 0.77 to 0.97) and 0.83 (95% CI: 0.73 to 0.94), respectively.

Details of the agreements are shown on Tables 1 and 2. Intra- and inter-observer agreements for Scores 2 and 3 showed a perfect match.

Overall results of visual thymic scoring are that 1869 (74%) showed complete fatty replacement of the thymus (Score 0), 463 (18%) predominantly fatty attenuation (Score 1), 172 (7%) half fatty and half soft-tissue attenuation (Score 2), and 36 (1%) solid thymic gland with predominantly soft-tissue attenuation (Score 3).

Associations between thymic scores and participants' characteristics are shown in Table 3. Participants with the lowest thymic score, indicating more fat content (Score 0) were significantly older (mean 61.7 years, $P<0.001$), more likely to be former smokers (49%, $P<0.001$) with higher pack-years (mean 20.3 p-y, $P=0.04$), and have a higher BMI (mean 29.3, $P<0.001$) than those with higher scores, indicating less fat and more soft tissue. Participants with the highest thymic score (Score 3) were more frequently female (86%, $P<0.001$) and more likely to have never smoked (64%, $P<0.001$).

The distribution of thymic scores in each sex and age group is shown in Table 4 and Figure 3. Overall, there was a significant negative correlation between thymic score and age (Correlation coefficient, -0.41 ; $P<0.001$). Female participants were given higher thymic scores than male overall ($P<0.001$). The sex difference in thymic score was significant in the age groups of 40-49 ($P<0.001$), 50-59 ($P<0.001$), and 60-69 ($P<0.001$) (Table 4). It was not significant in the age groups of 39 or younger ($P=0.95$) as well as 70-79 ($P=0.32$) and 80 or older ($P=0.67$). In the age group of 39 or younger, there were only 9 female and 41 male participants.

A summary of thymic measurements from 671 cases (408 females and 263 males) with thymic scores 1-3 is shown in Table 5. There was a significant correlation between CT attenuation and age for both female and male ($P<0.001$). In male, all the variables of thymic size measurement showed no significant correlation with age ($P=0.4-0.8$). In female, AP diameter ($P=0.04$) and length of the right lobe ($P=0.001$) showed significant correlation with age, but other variables of thymic size were not significant ($P=0.05-0.2$). There were significant differences in measurements in each variable between female and male participants ($P<0.001$ for all). Figure 4 demonstrates the negative correlation between CT attenuation and age. CT attenuation in female (mean, -39.3 HU; SD, 27.6) shows higher values than that in male (mean, -51.7 HU; SD, 27.6).

The most frequently seen morphology of the thymus was pyramidal with straight margin (477/671, 71%), followed by pyramidal with convex margin (147/671, 22%), pyramidal with concave margin (27/671, 4%), and irregular (20/671, 3%).

DISCUSSION

The present study investigated the normal appearance of the thymus in middle aged and older adults in a large cohort from the general population. The visual assessment with a four-point scale revealed the sex difference in thymic appearance on CT in the age of 40-69. Cigarette smoking and high BMI are associated with advanced fat degeneration of the thymic gland.

Intra- and inter-observer agreements of the four-point scale thymic scoring system were excellent with weighted Cohen κ values of 0.87 and 0.83, respectively. This method originally reported by Ackman et al was sufficiently reproducible in middle and older age groups in our study as well as in their original study group at age of 20-30 years with weighted Cohen κ values of 0.95 [6].

Our study demonstrated a spectrum of appearance of a normal thymus on CT and the sex difference in the middle and older age groups. In the present cohort from the FHS with the mean age of 58.9 years, only 8% (208/2540) of overall participants had thymic glands with half or more soft-tissue parenchyma (Scores 2 and 3), and 74% (1869/2540) showed a complete fatty replacement of the thymic gland due to advanced involution. Barron et al reported that 83% of participants aged 50 and older demonstrated no visible thymic gland on CT images [3], which is similar to our results of 82% (1548/1882) with complete fatty replacement in the same age group (Table 4). Simanovsky et al reported that 71% (138/194) of the trauma patients with mean age of 52.6 showed complete fat replacement of the thymus [5]. They also reported that no solid tissue component was seen in patients older than 54 years [5]. However, in our study soft tissue component of the thymus was seen in 9% (104/1111) of the participants older than 60 years. The four-point scale visual assessment of the thymic gland negatively correlates to participant age ($P<0.001$), indicating that the assessment can be used as a benchmark of thymic involution when we discuss the normality of the thymus. In a recent study using chemical shift MRI, Priola et al suggested that an increase of fat tissue with age might occur in hyperplastic thymus, as occurs in normal thymus [17]. Therefore, further study is necessary to assess the usefulness of thymic scores or other qualitative parameters in differentiation of normal thymus and hyperplasia.

The sex difference in thymic scores was significant in participants from 40 to 69 years of age; female participants in this age range showed thymic glands with less fatty contents than male. This was also demonstrated with actual measurement of CT attenuation (Figure 4). In the recent study by Ackman et al which investigated 20-30 year-old patients, male showed more rapid fatty intercalation than female [6]. These findings suggest that the onset of thymic involution in women is delayed by approximately 10 to 20 years in comparison to men. Thymic involution is completed by the age of 60 in men and 70 in women, and the sex difference in the thymic appearance seems to eventually fade away by the age of 70. Sex steroids are considered to be an important factor for the sex difference of the thymus [6]. A previous animal study suggested that progesterone might play an important role in thymic involution during pregnancy [18]. Although the present study did not investigate the issue, the drastic changes in hormonal status in women, such as pregnancy and menopause, might contribute to the sex difference of thymic degeneration.

In addition to age and sex, our results reveal that thymic scores are associated with smoking status and BMI. Participants with a fatty degenerated thymus (Score 0) are more likely to be former smokers (49%). On the other hand, those with a solid thymus (Score 3) are more likely to have no primary exposure to cigarette smoking (64%). Number of pack-years in participants with a complete fat-replaced thymus (Score 0; mean, 20.3 p-y) was significantly higher than in those with a solid thymus (Score 3; mean 6.8 p-y) ($P<0.001$). Zeyrek et al reported that smoking during pregnancy results in a smaller thymus of the newborn [19];

however, the effect of smoking on the adult thymus has not been understood. Our results suggest that cigarette smoking may facilitate fatty degeneration of the thymus. However, further investigation with longitudinal observation is necessary to reveal the exact mechanism by which cigarette smoking affects the thymic gland.

Participants with lower thymic scores also showed significantly higher BMI compared to those with higher thymic scores ($P < 0.001$, Table 3). Obesity is associated with an increased risk of infection. Animal studies demonstrate that obesity might cause premature involution and fat accumulation of the thymus, resulting in a decline of naive T-cell production in the thymic gland [20, 21]. Yoshida et al investigated a large cohort with 1073 human subjects and suggested that high BMI is associated with a decline of T-cell production. Although they did not directly investigate fat depositions in the thymus, based on the above-mentioned animal studies it is likely that high BMI is associated with increased amount of fat tissue in the thymus [22], which we observed on CT in the present study. Therefore, our results are consistent with these prior reports. Another consideration could be that obese subjects might have the thymus gland with more fat tissues interspersed, which may occur in muscle fiber bundles.

In the present study, meticulous measurements of the thymic glands revealed that those in male were significantly larger than those in female, thus justifying the data split according to sex, providing reference values for the size of a normal thymus. However, it should be noted that thymus glands at middle and older age, especially in male, are usually not applicable for measurements because of advanced fatty degeneration with an obscured contour. Moore et al suggested that the overall size of the thymus may not change with aging in adults [3, 23]. Also, in the present study, no significant correlation was detected between thymic size and age, except for AP diameter and length of the right lobe in female. Visual assessment with thymic scores would be a better index of thymic involution rather than quantitative measurements.

In previous studies, the shape of the normal thymus was described as bilobed, triangular, pyramidal, arrowhead, or quadrilateral [1, 3-6, 23-25]. Pyramidal with straight margin was the most frequently seen morphology in our study. Although a convex margin may suggest a hyperplastic thymus [13], a normal thymus can also often have a convex margin; 22% showed a convex margin in our study. The shape of the thymus is complex in three dimensions and often asymmetrical with a predominant left lobe [3, 6]. Furthermore, since the thymus is located as if it filled the space between the major vessels in the mediastinum and the lateral margins of both lobes are endorsed with the anteromedial surface of the lungs, it is apparent that these surrounding structures affect thymic morphology [5]. Therefore, we surmise that thymic morphology may play a limited role in defining the normality of the thymus.

There are several limitations in the present study, including a cross-sectional review of CT scans instead of longitudinal observation of participants, and non-uniform distribution of age and sex in the cohort. Although the numbers of female and male participants were nearly equal, the younger age group had fewer female, and the older age group had more female participants. The number of participants at age 39 and younger was probably too small to

draw a statistically significant result. Second, some critics suggest that participants in the FHS may not exactly represent the general population because they may be healthier due to high health consciousness and significant medical support. However, the FHS population of supposedly healthy participants with chest CT imaging performed without any clinical intention along with thorough collection of demographic information provides a unique opportunity to investigate the normal thymus. Third, our results rely mostly on the evaluation and measurement by a single reader based on the excellent intra- and inter-observer agreements shown in our preliminary study and the previous report by Ackman et al [6] as well as our previous investigation of the variability in quantitative measurements of the thymus [12]. Lastly, clinical information specifically associated with thymic diseases is limited, such as autoimmune disease, in particular myasthenia gravis, thyroid diseases, malignancies, and treatment history with steroid and antineoplastic drugs [1, 26]. Therefore, in the present study the possibility of inclusion of thymic hyperplasia could not be totally excluded.

In conclusion, visual assessment using four-point thymic scores revealed a normal spectrum of the thymus and a sex difference in the fatty degeneration of the thymus with age. The thymus in women shows less fatty content at age 40-69 than that in men, suggesting delayed onset and progression in thymic involution in women. Cigarette smoking and high BMI are associated with advanced fatty replacement of the thymic gland.

Acknowledgement

Authors acknowledge Alba Cid M.S. for editorial work on the manuscript.

Dr. Nishino is supported by NCI Grant Number: 1K23CA157631. Dr. Washko is supported by NIH Grant Number: R01 HL116473, R01 HL107246 and P01 HL114501. Dr. Hunninghake is supported by NIH Grant Number: K08 HL092222, U01 HL105371, P01 HL114501, and R01 HL111024. Dr. Hatabu is supported by NIH Grant Number: K25 HL104085 and R01 HL116473. This work was partially supported by the NHLBI's Framingham Heart Study contract: N01-HC-25195 and R01 HL111024.

Abbreviations

CT	computed tomography
BMI	body mass index
FHS	Framingham Heart Study

References

1. Nishino M, Ashiku SK, Kocher ON, Thurer RL, Boisselle PM, Hatabu H. The Thymus: A Comprehensive Review. *Radiographics*. 2006; 26(2):335–48. [PubMed: 16549602]
2. Suster S, Rosai J. Histology of the normal thymus. *Am J Surg Pathol*. 1990; 14(3):284–303. [PubMed: 2407143]
3. Baron R, Lee J, Sagel S, Peterson R. Computed tomography of the normal thymus. *Radiology*. 1982; 142(1):121–5. [PubMed: 7053521]
4. Francis I, Glazer G, Bookstein F, Gross B. The thymus: reexamination of age-related changes in size and shape. *American Journal of Roentgenology*. 1985; 145(2):249–54. [PubMed: 3875220]
5. Simanovsky N, Hiller N, Loubashevsky N, Rozovsky K. Normal CT characteristics of the thymus in adults. *European Journal of Radiology*. 2012; 81(11):3581–6. [PubMed: 22236705]

6. Ackman JB, Kovacina B, Carter BW, Wu CC, Sharma A, Shepard JA, et al. Sex difference in normal thymic appearance in adults 20-30 years of age. *Radiology*. 2013; 268(1):245–53. [PubMed: 23440318]
7. Henschke CI, Lee JJ, Wu N, Farooqi A, Khan A, Yankelevitz D, et al. CT screening for lung cancer: prevalence and incidence of mediastinal masses. *Radiology*. 2006; 239(2):586–90. [PubMed: 16641357]
8. Priola AM, Priola SM, Giaj-Levra M, Basso E, Veltri A, Fava C, et al. Clinical implications and added costs of incidental findings in an early detection study of lung cancer by using low-dose spiral computed tomography. *Clinical Lung Cancer*. 2013; 14(2):139–48. [PubMed: 22868220]
9. Araki T, Nishino M, Gao W, Dupuis J, Washko GR, Hunninghake GM, et al. Anterior mediastinal masses in the Framingham Heart Study: Prevalence and CT image characteristics. *European Journal of Radiology Open*. 2015; 2:26–31. [PubMed: 25705709]
10. Mendis S. The contribution of the Framingham Heart Study to the prevention of cardiovascular disease: a global perspective. *Progress in Cardiovascular Diseases*. 2010; 53(1):10–4. [PubMed: 20620420]
11. Sopori M. Effects of cigarette smoke on the immune system. *Nature Reviews Immunology*. 2002; 2(5):372–7.
12. Araki T, Sholl LM, Gerbaudo VH, Hatabu H, Nishino M. Thymic Measurements in Pathologically Proven Normal Thymus and Thymic Hyperplasia: Intraobserver and Interobserver Variabilities. *Academic Radiology*. 2014; 21(6):733–42. [PubMed: 24809315]
13. Araki T, Sholl LM, Gerbaudo VH, Hatabu H, Nishino M. Imaging characteristics of pathologically proven thymic hyperplasia: identifying features that can differentiate true from lymphoid hyperplasia. *AJR American Journal of Roentgenology*. 2014; 202(3):471–8. [PubMed: 24555583]
14. Jin GY, Lynch D, Chawla A, Garg K, Tammemagi MC, Sahin H, et al. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology*. 2013; 268(2):563–71. [PubMed: 23513242]
15. Kundel HL, Polansky M. Measurement of observer agreement. *Radiology*. 2003; 228(2):303–8. [PubMed: 12819342]
16. Uh HW, Wijk HJ, Houwing-Duistermaat JJ. Testing for genetic association taking into account phenotypic information of relatives. *BMC proceedings*. 2009; 3(Suppl 7):S123. [PubMed: 20017989]
17. Priola AM, Priola SM, Ciccone G, Evangelista A, Cataldi A, Gned D, et al. Differentiation of rebound and lymphoid thymic hyperplasia from anterior mediastinal tumors with dual-echo chemical-shift MR imaging in adulthood: reliability of the chemical-shift ratio and signal intensity index. *Radiology*. 2015; 274(1):238–49. [PubMed: 25105246]
18. Tibbetts TA, DeMayo F, Rich S, Conneely OM, O'Malley BW. Progesterone receptors in the thymus are required for thymic involution during pregnancy and for normal fertility. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96(21):12021–6. [PubMed: 10518569]
19. Zeyrek D, Ozturk E, Ozturk A, Cakmak A. Decreased thymus size in full-term newborn infants of smoking mothers. *Medical Science Monitor : international medical journal of experimental and clinical research*. 2008; 14(8):CR423–6. [PubMed: 18668000]
20. Yang H, Youm YH, Vandanmagsar B, Rood J, Kumar KG, Butler AA, et al. Obesity accelerates thymic aging. *Blood*. 2009; 114(18):3803–12. [PubMed: 19721009]
21. Gulvady AA, Ciolino HP, Cabrera RM, Jolly CA. Resveratrol inhibits the deleterious effects of diet-induced obesity on thymic function. *The Journal of Nutritional Biochemistry*. 2013; 24(9):1625–33. [PubMed: 23561698]
22. Yoshida K, Nakashima E, Kubo Y, Yamaoka M, Kajimura J, Kyoizumi S, et al. Inverse associations between obesity indicators and thymic T-cell production levels in aging atomic-bomb survivors. *PLOS ONE*. 2014; 9(3):e91985. [PubMed: 24651652]
23. Moore AV, Korobkin M, Olanow W, Heaston DK, Ram P, Dunnick N, et al. Age-related changes in the thymus gland: CT-pathologic correlation. *American Journal of Roentgenology*. 1983; 141(2):241–6. [PubMed: 6603111]

24. Niendorf ER, Parker JA, Yechoor V, Garber JR, Boisselle PM. Thymic hyperplasia in thyroid cancer patients. *Journal of Thoracic Imaging*. 2005; 20(1):1–4. [PubMed: 15729115]
25. Nishihara M. [CT of the thymus--I. CT image of the normal thymus]. *Nihon Igaku Hoshasen Gakkai Zasshi Nippon Acta Radiologica*. 1987; 47(6):799–803. In Japanese. [PubMed: 3684520]
26. Shimosato, Y.; Mukai, K.; Matsuno, Y. Tumors of the mediastinum; AFIP Atlas of Tumor Pathology 4th Series Fascicle 11. ARP PRESS; Silver Spring, Maryland: 2010.

Key Points

1. 74% of participants (Mean age 58.9 years) demonstrated complete fatty thymus.
2. Women show less fatty thymus compared to men in age 40-69.
3. Smoking and high BMI are associated with advanced fatty degeneration in thymus.

Figure 1. Representative CT images of each thymic score

Each row of axial CT images represents each thymic score of two different participants (0 to 3, from the top to bottom rows). (a) A complete fatty degeneration of thymic gland (Score 0) in a 79-year-old female. (b) Another example of complete fatty degeneration (Score 0) in a 65-year-old male. Spotty nodules are detectable, however, with paging of images, which revealed to be fine blood vessels in the anterior mediastinum. (c) A thymic gland with predominantly fat density (Score 1) in a 62-year-old female. Reticulonodular remnants of the thymus are seen. (d) Another example of a thymic gland with predominantly fat density

(Score 1) in a 72-year-old male. Fine nodules of thymic remnants and partial soft-tissue density in the left lobe are seen. (e) A triangular thymic gland with half solid tissue and half fat attenuation (Score 2) in a 51-year-old male. The left lobe is extending posterolaterally. (f) A triangular shaped thymic gland with half fatty degeneration (Score 2) in a 63-year-old female. (g) A solid triangular thymic gland (Score 3) in a 43-year-old female. (h) A predominantly soft-tissue attenuated thymic gland (Score 3) with minimal spotted fat in a 43-year-old female.

Figure 2. Measurement method of the thymic size, including anteroposterior (AP) and transverse diameters, length and thickness of each lobe. (With modification from References [12, 13])

Figure 3. Distribution of thymic score by sex and age groups

Bar plots represent frequency of each thymic score by each age group. Vertical lines extending from each plot indicate 95% CI (confidence interval) with horizontal lines for the upper and lower limits. 95% CI was determined by using an exact binominal approach.

Figure 4.
Scatter plots of CT attenuation versus age with the fitted regression lines

Table 1

Intra-observer agreement of thymic score

		Observer 1 (First)				
	Thymic score	0	1	2	3	Total
Observer 1 (Second)	0	74	7	0	0	81
	1	0	13	0	0	13
	2	0	0	2	0	2
	3	0	0	0	4	4
Total		74	20	2	4	100

For intra-observer agreement between the two sets of scores by one radiologist, the weighted Cohen κ value was 0.87 (95% CI: 0.77 to 0.97).

Table 2

Inter-observer agreement of thymic score

		Observer 2				
	Thymic score	0	1	2	3	Total
Observer 1	0	66	8	0	0	74
	1	2	18	0	0	20
	2	0	0	2	0	2
	3	0	0	0	4	4
Total		68	26	2	4	100

For inter-observer agreement between two radiologists, the weighted Cohen κ value was 0.83 (95% CI: 0.73 to 0.94)

Table 3

Characteristics of participants based on thymic score

	Thymic Score				P Value ^{†,‡}
	0 (N=1869)	1 (N=463)	2 (N=172)	3 (N=36)	
Age — year	61.7 ± 11.7	51.2 ± 8.6	50.8 ± 8.4	47.0 ± 7.6	<0.001
Female sex — no. (%)	888 (48)	261 (56)	116 (67)	31 (86)	<0.001
Body-mass index (kg/m ²) [*]	29.3 ± 5.5 (N=1856)	26.7 ± 4.6 (N=462)	25.3 ± 4.1	23.8 ± 3.5	<0.001
Smoking status —no. (%)					
Never	823 (44)	275 (60)	108 (63)	23 (64)	<0.001
Former	912 (49)	154 (33)	55 (32)	10 (28)	<0.001
Current	117 (6) (N=1852)	31 (7) (N=460)	8 (5) (N=171)	3 (8)	0.8
Pack-year	20.3 ± 18.7 (N=965)	12.8 ± 14.1 (N=174)	11.1 ± 11.6 (N=60)	6.8 ± 12.2 (N=10)	0.04

Plus-minus values are mean ± standard deviation.

Percentages may not add to 100 due to rounding.

^{*} The body-mass index (BMI) is calculated with the following equation: $BMI = \frac{\text{body weight (kg)}}{\text{height (m)}^2}$

[†] P values were calculated with the use of linear mixed effect models or generalized estimating equations to account for familial relationships in the Framingham Heart Study, as described previously [16].

[‡] P values for BMI, smoking status, and pack-year were the results of analyses adjusted for age and sex. In addition, P values for BMI and pack-year were also adjusted for pack-year and BMI, respectively.

Table 4

Thymic scores by sex and age group

Thymic Score		Age Group (year)						Total
		39	40-49	50-59	60-69	70-79	80	
0	Female	2 (22)	94 (39)	221 (55)	302 (84)	196 (96)	73 (95)	888
	Male	9 (22)	216 (59)	300 (82)	240 (96)	163 (98)	53 (96)	981
	Subtotal	11 (22)	310 (51)	521 (68)	542 (89)	359 (97)	126 (96)	1869
1	Female	4 (44)	88 (36)	126 (31)	31 (9)	8 (4)	4 (5)	261
	Male	22 (54)	109 (30)	57 (16)	10 (4)	2 (1)	2 (4)	202
	Subtotal	26 (52)	197 (32)	183 (24)	41 (7)	10 (3)	6 (5)	463
2	Female	2 (22)	43 (18)	46 (11)	24 (7)	1 (0.5)	0 (0)	116
	Male	7 (17)	37 (10)	11 (3)	0 (0)	1 (0.6)	0 (0)	56
	Subtotal	9 (18)	80 (13)	57 (7)	24 (4)	2 (0.5)	0 (0)	172
3	Female	1 (11)	19 (8)	10 (3)	1 (0.3)	0 (0)	0 (0)	31
	Male	3 (7)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	5
	Subtotal	4 (8)	21 (4)	10 (1)	1 (0.2)	0 (0)	0 (0)	36
Total	Female	9	244	403	358	205	77	1296
	Male	41	364	368	250	166	55	1244
	Subtotal	50	608	771	608	371	132	2540
P Value [†]		0.95	<0.001	<0.001	<0.001	0.32	0.67	<0.001

Numbers within parentheses are percentage in the column.

Percentages may not add to 100 due to rounding.

Shaded numbers indicate less than five percent in frequency.

[†]P values are for comparison of thymic scores between female and male.

Table 5

Summary of thymic measurements by sex and age groups

Female							
Age Group (year)	Means of Thymic Measurements						
	AP Diameter (mm)	Transverse Diameter (mm)	Lt Length (mm)	Lt Thickness (mm)	Rt Length (mm)	Rt Thickness (mm)	CT Attenuation (HU)
39 (n=7)	26.2 ± 7.7	29.7 ± 9.3	30.5 ± 11.3	9.4 ± 2.3	20.6 ± 5.7	10.2 ± 4.2	-36.3 ± 30.0
40-49 (n=150)	23.0 ± 7.4	30.3 ± 8.4	28.8 ± 9.0	9.4 ± 3.1	19.1 ± 6.7	9.9 ± 3.6	-32.1 ± 30.7
50-59 (n=182)	23.1 ± 8.9	30.6 ± 9.8	29.2 ± 10.0	9.0 ± 3.3	18.3 ± 6.9	9.9 ± 3.8	-43.0 ± 24.6
60-69 (n=56)	20.8 ± 7.0	29.6 ± 7.9	27.5 ± 8.6	8.7 ± 3.3	16.7 ± 5.5	8.7 ± 2.6	-43.0 ± 25.6
70-79 (n=9)	22.8 ± 6.6	28.1 ± 5.5	28.5 ± 9.9	8.5 ± 2.3	16.1 ± 3.7	8.7 ± 2.1	-58.1 ± 20.9
80 (n=4)	16.0 ± 7.7	20.8 ± 5.1	19.8 ± 6.5	6.7 ± 2.9	12.3 ± 3.9	8.6 ± 3.6	-52.2 ± 15.7

Male							
Age Group (year)	Means of Thymic Measurements						
	AP Diameter (mm)	Transverse Diameter (mm)	Lt Length (mm)	Lt Thickness (mm)	Rt Length (mm)	Rt Thickness (mm)	CT Attenuation (HU)
39 (n=32)	30.8 ± 7.8	36.9 ± 10.0	36.4 ± 8.4	12.6 ± 3.6	25.6 ± 8.8	13.6 ± 4.4	-41.9 ± 27.9
40-49 (n=148)	28.6 ± 8.6	36.2 ± 11.0	35.2 ± 9.6	11.3 ± 4.0	23.0 ± 9.1	12.7 ± 4.7	-49.7 ± 22.2
50-59 (n=68)	29.5 ± 9.7	37.6 ± 9.5	36.5 ± 11.0	11.7 ± 3.8	23.5 ± 8.0	13.1 ± 4.4	-57.5 ± 20.8
60-69 (n=10)	30.5 ± 4.2	40.2 ± 8.3	38.4 ± 6.7	12.2 ± 4.3	22.9 ± 9.0	13.5 ± 5.9	-65.3 ± 18.6
70-79 (n=3)	33.4 ± 13.8	44.4 ± 14.9	43.3 ± 21.5	10.8 ± 2.7	28.2 ± 13.6	12.1 ± 1.8	-67.2 ± 16.4
80 (n=2)	25.2 ± 10.4	31.5 ± 3.1	33.0 ± 8.0	9.4 ± 0.9	22.3 ± 6.9	11.4 ± 3.0	-76.5 ± 0.3

Plus-minus values are mean ± standard deviation.

AP, anteroposterior diameter; Lt, left; Rt, right.

Plus-minus values are mean ± standard deviation.

AP, anteroposterior diameter; Lt, left; Rt, right.